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Dennis J. Paustenbach

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ASSESSMENT OF THE DEVELOPMENTAL RISKS RESULTING FROM OCCUPATIONAL EXPOSURE TO SELECT GLYCOL ETHERS WITHIN THE SEMICONDUCTOR INDUSTRY

Dennis J. Paustenbach

McLaren-Chemrisk, Rancho Cordova, California

This risk assessment evaluates the potential human hazards of adverse developmental effects posed by exposure to 2-ethoxyethanol (2-EE), 2-ethoxyethanol acetate (2-EEA), 2-methoxyethanol (2-ME), and 2-methoxyethanol acetate (2-MEA) as they are currently used in semiconductor manufacturing. These glycol ethers are contained in positive photoresists used in the wafer fabrication process. The available data on the developmental toxicology of these glycol ethers indicates that each can selectively affect the offspring of pregnant animals that have been exposed to relatively low vapor concentrations. For these chemicals, the ratio of the lowest dose which adversely affected the pregnant animals (A) and the lowest dose which produced developmental effects in offspring (D), e.g., A/D ranged from 1–5. Approximately 400 workplace air samples of 4–8 h duration, both personal and area, from seven different companies were used to assess the degree of inhalation exposure during the manufacture of wafers. The geometric mean results obtained during personal sampling of workplace air for 2-EE, 2-EEA, 2-ME, and 2-MEA were 0.36, 0.02, 0.10, and 0.01 ppm, respectively. These levels are 14- to 500-fold lower than the applicable threshold limit value (TLV) currently recommended by the American Conference of Governmental Industrial Hygienists (ACGIH). Specifically, the margins of safety between the typical occupational exposure and the TLV for 2-ME, 2-EE, 2-MEA, and 2-EEA are 50, 14, 500, and 250, respectively. The TLVs for these chemicals were set at levels considered sufficiently low to protect workers and their offspring from adverse effects and are about 2- to 10-fold lower than the various no-observed-effect levels (NOELs) obtained in animal tests. Based on more recent data, lower TLVs are indicated. The safety-factor approach, rather than mathematical models developed for estimating cancer risks, was used in this analysis. Historical data have shown that the application of safety factors of 10–100 to the NOEL, as determined in Segment II developmental toxicology tests in animals, should be adequate to protect humans. In its risk assessment guidelines, the U.S. Environmental Protection Agency (EPA) selected the uncertainty-factor approach as the most reasonable one for evaluating the hazards of developmental toxicants. This assessment indicates that the airborne concentrations of these glycol ethers in the semiconductor industry are, in general, sufficiently low to protect employees against their adverse developmental and reproductive effects as well as any other toxic effects as long as dermal exposure is minimal.

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Requests for reprints should be sent to Dennis J. Paustenbach, McLaren-Chemrisk, 11101 White Rock Road, Rancho Cordova, California 95670.

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INTRODUCTION

In recent years, the public has expressed an increasing concern for those chemicals used in the workplace and the home that have been shown to adversely affect offspring in animal tests (Adler, 1987). Once known as teratology tests, these toxicological studies have been more appropriately defined as tests for developmental toxicity (Nisbet and Karch, 1983; Environmental Protection Agency, 1986; Johnson, 1984; Fabro, 1985). Such tests attempt to identify those chemicals that can cause growth retardation, reduced viability, malformations, and functional impairment in the offspring of exposed animals (Wilson, 1973a,b; Johnson and Christian, 1984). Following the identification of those substances that could alter development, the risk posed by the various proposed uses should be evaluated, human exposure measured, control measures considered, and risk-management decisions reached (National Research Council, 1983).

Although the risk assessment process has frequently been used to evaluate carcinogenic substances (Gehring et al., 1978; Starr and Buck, 1984; Turnbull and Rodricks, 1985; Andersen et al., 1987), few, if any, risk assessments of chemicals that produce developmental effects in animals have been published in the open literature (Fabro, 1985). In 1986, the U.S. Environmental Protection Agency (EPA) published risk-assessment guidelines for developmental toxicants, and these represent good criteria on which to develop such analyses (EPA, 1986). The EPA document concluded that it is currently assumed that a threshold exists for developmental toxicants because "the embryo is known to have some capacity for repair of the damage or insult and that most developmental deviations are probably multifactorial in nature." Accordingly, the EPA indicated that safety factors are generally used to evaluate human risk, since there are no theoretical grounds for adopting mathematical models that are currently used to assess genotoxic carcinogens (EPA, 1986). The safety-factor approach has been previously recommended (Wilson, 1973a; Hogan and Hoel, 1982; Johnson, 1984; Fabro, 1985).

The simple evaluation of whether a chemical has the capacity to affect the offspring of humans based on animal data has been termed a "qualitative assessment" (Food Safety Council, 1980). The objective of this process is to determine whether a chemical "could" pose a particular hazard to humans. In contrast, a "quantitative assessment" is the process by which the likelihood of an adverse effect (e.g., a developmental effect) at a given dose is evaluated. Risk assessments are both qualitative and quantitative. They should incorporate all available data regarding the chemical and physical properties of the chemical, its potency, magnitude of the exposure, timing of the exposure, mechanism of action, and its pharmacokinetic behavior. Interestingly, risk assessments of developmental agents, unlike the assessment of carcinogens, are fur-

ther complicated because the "timing" of the exposure, as well as the type and severity of the untoward response, must also be considered. Further, the chemical's dose-response curve for both the mother and the offspring should be understood (EPA, 1986).

The EPA guidelines (1986) noted that "approaches to ranking agents for their selective developmental toxicity have been proposed, and these have been reviewed by Schardein (1983). Of current interest are those that develop ratios relating an adult toxic dose with the dose that affects fetal development (Johnson, 1981; Rao and Schwetz, 1981; Fabro et al., 1982; Johnson and Gabel, 1983; Johnson, 1987; Johnson, 1988). Ratios near unity indicate that developmental toxicity occurs only at doses producing maternal toxicity; as the ratio increases, there is a greater likelihood of developmental effects occurring without maternal toxicity." The latter phenomenon are known as developmental phase-specific effects (Horton et al., 1985). Although further validation is necessary (Holson et al., 1981), such approaches should ultimately help identify those agents that are likely to pose the greatest threat to the health of human offspring and help establish priorities (Johnson, 1987).

In spite of the numerous uncertainties associated with any risk assessment, especially those dealing with agents that may affect offspring, the application of safety factors to the NOELs obtained in Segment II studies represents the best available approach for objectively evaluating the likelihood of adverse health effects following a certain level of exposure to a xenobiotic. The benefits of using risk assessments to address difficult environmental issues have been demonstrated on numerous occasions (Rodricks and Taylor, 1983; Ruckelshaus, 1984). Since virtually any chemical or drug—when a proper dose is administered, at the proper stage of development, to embryos of the proper species—will be effective in producing adverse developmental effects on the fetus (known as Karnofsky's law), the risk-assessment process is particularly relevant to developmental toxins (Karnofsky, 1965). Such assessments are important since they bring together the results of all pertinent toxicology tests, metabolism studies, and exposure assessments, and then integrates them into a cohesive document upon which a risk-management decision can be reached (Lave, 1982; Ruckelshaus, 1984). From such assessments, managers and scientists within federal or state agencies, industry, and the public can make informed decisions. Assessments can also identify those areas where more scientific data are needed.

The public and scientific interest in the glycol ethers, and especially 2-methoxyethanol (2-ME), 2-methoxyethanol acetate (2-MEA), 2-ethoxyethanol (2-EE), and 2-ethoxyethanol acetate (2-EEA), has been to a large extent, brought about by toxicology research that indicated that these chemicals can cause developmental effects in the offspring of exposed animals (Hardin et al., 1982; Brown et al., 1984; Nelson et al.,

1982, 1984a; Tinston et al., 1983a–e; Hanley et al., 1982a,b; Nelson and Brightwell, 1984; Horton et al., 1985; Ritter et al., 1985; John et al., 1984; Tyl et al., 1984, 1987). Broadscale interest in these compounds has been spurred by the EPA's risk assessment of 2-methoxyethanol, 2-ethoxyethanol, and their acetates (EPA, 1984) and by the interest of the Occupational Safety and Health Administration (NIOSH, 1983; *Chemical Regulation Reporter,* 1986). their acute toxicity has been well defined for a number of years (Morris et al., 1942; Werner et al., 1943a–c; Carpenter and Smyth, 1946; Carpenter et al., 1956; Flury and Wirth, 1943).

A number of clinical reports describing the acute toxic effects of fairly heavy exposure to the glycol ethers were published about 50 yr ago (Donlet, 1936; Parsons and Parsons, 1938; Greenburg et al., 1937a,b; Greenburg, 1937). Although these studies showed that the glycol ethers could cause depression of the central nervous system and hematopoetic effects, the available data suggest that exposure to airborne concentrations less than 25 ppm for 8 h/d would not be expected to produce acute adverse effects. Reports by Zavon (1963) and Ohi and Wegman (1978) described toxicity from 2-ME following exposure when it was used as a printing and ink solvent. Both studies suggested that dermal uptake was an important route of entry. Cohen (1984) has observed that inhalation exposures of about 35 ppm of 2-ME coupled with dermal uptake can produce adverse effects on the hematopoetic system.

In a study of males exposed to 25 ppm of 2-EE in the manufacture of castings, an apparent decrease in the average sperm count was observed (NIOSH, 1986). A case report of males exposed to 2-ME and 2-EE suggested that semen quality may have been affected (Welch et al., 1988). Epidemiological studies of the reproductive outcome of workers exposed to low levels of the glycol ethers have not demonstrated an adverse effect (Cook et al., 1982; Pastides and Calabrese, 1987a). Nonetheless, some firms have chosen to limit or eliminate women of childbearing age from jobs where exposure to select glycol ethers is possible (Anonymous, 1987a).

This paper evaluates the developmental and reproductive hazards posed by the four most commonly used glycol ethers in the semiconductor industry. Concern has been expressed over the 20,000 persons who are potentially exposed to these chemicals within this industry (La Dou, 1984; La Dou, 1985; Harper, 1986; *Chemical Regulation Reporter,* 1986; Anonymous, 1987a,b). As is customary in developing a risk assessment, the available toxicity data (e.g., hazard characterization) and industrial hygiene sampling results from this industry (e.g., exposure assessment) were used to evaluate the likelihood that these exposures could produce adverse effects in these workers or their offspring. Wherever appropriate, the terminology and methodologies for assessing risk that have been proposed by the EPA (1986) have been used.

TABLE 1. Evaporation Rate of Ethylene Oxide-Based Glycol Ethers

Solvents	Relative evaporation rate[a] (*n*-butyl acetate = 1)	Flash point[b] TCC (°F)
Ethylene glycol	0.0001	232
Ethylene glycol monomethyl ether (EGME or 2-ME)	0.5	120
Ethylene glycol monoethyl ether (EGEE or 2-EE)	0.3	115
Ethylene glycol monopropyl ether (EGPE or 2-PE)	0.2	125
Ethylene glycol monobutyl ether (EGBE or 2-BE)	0.07	165
Ethylene glycol monomethyl ether acetate (EGMEA or 2-MEA)	0.3	140
Ethylene glycol monoethyl ether acetate (EGEEA or 2-EEA)	0.2	150

[a]From Smith (1984) or Rowe and Wolfe (1982).
[b]From Rowe and Wolfe (1982) or Olishifski (1979).

THE GLYCOL ETHERS: CHARACTERISTICS AND USE

The ethylene glycol ethers are a family of chemicals derived from ethylene oxide. The glycol ethers possess numerous physical properties that are different from the more commonly used ethylene glycol, known as antifreeze. Of the glycol ethers, the 2-methoxyethanol (2-ME) is the most common and approximately 90 million pounds of the 2-ME were sold in 1981 in the United States alone (Rowe and Wolfe, 1982). The importance and use of glycol ethers and glycol ether esters in the coatings and semiconductor industries has been reviewed by Smith (1984).

Glycol ether solvents were first introduced as commercial products in the late 1920s. Because *n*-butyl acetate was the primary solvent used in coatings, the introduction of the glycol ether solvents represented a major improvement for the coatings industry. Of the commercially available ethylene oxide-based glycol ethers and glycol ether ester solvents (Table 1), ethylene glycol monomethyl ether or 2-methoxyethanol (EGME or 2-ME), ethylene glycol monoethyl ether or 2-ethoxyethanol (EGEE or 2-EE), ethylene glycol monopropyl ether or 2-propyl ether (EGPE or 2-PE), ethylene glycol monobutyl ether or 2-butoxyethanol (EGBE or 2-BE), ethylene glycol monomethyl ether acetate or 2-methoxyethyl acetate (EGMEA or 2-MEA), and ethylene glycol monoethyl ether acetate or 2-ethoxyethyl acetate (EGEEA or 2-EEA) all have evaporation rates between 0.5 and 0.07 (see Table 1). The use of 2-ME and 2-MEA is generally limited to specialty appliances in the coatings and the semiconductor industries, but the other products (EGEE, EGPE, EGBE and EGEEA) all have a broad range of uses in the coatings industry (Smith, 1984). As determined by the tag

TABLE 2. Vapor Pressures, Vapor Hazard Indices (VHI) and Occupational Exposure Limits for Select Glycol Ethers and Several Other Common Industrial Solvents

Chemical	Vapor pressure at 25°C (mm Hg)	OSHA PEL[a] (ppm)	ACGIH TLV[b] (ppm)	Vapor hazard index (PEL)[c]	Vapor hazard index (TLV)[d]
2-Methoxyethanol	10	25	5	0.40	2.00
2-Methoxyethanol acetate	5	25	5	0.20	1.00
2-Ethoxyethanol	5.3	200	5	0.03	1.00
2-Ethoxyethanol acetate	2	100	5	0.02	0.40
Acetone	227	1000	750	0.23	0.30
Methylene chloride	390	500	100	0.80	3.90
Perchloroethylene	19	100	50	0.20	0.38
Toluene	30	200	100	0.15	0.30

[a]OSHA permissible exposure limit (PEL). Based on CFR 1910. 1000 (1970).

[b]ACGIH threshold limit values (TLV), 1985-1986 values.

[c]Vapor hazard index (VHI) is defined as the vapor pressure (mm Hg) at 25°C divided by the occupational exposure limit. This index is useful for identifying which chemical, among a group used in a similar manner, is likely to be the most difficult to control to acceptable airborne levels. The higher the index, the greater the likelihood that the concentration will approach the exposure limit. In this column, the VHI is based on the OHSA PEL.

[d]Vapor hazard index based on 1985-1986 TLVs.

closed cup technique (Table 1), TCC, the flash points vary between 115° and 232°F (Olishifski, 1979).

Within the semiconductor industry, the glycol ethers are primarily used in the photolithographic portion of the wafer manufacturing process (Wald and Jones, 1987). One of several different types of glycol ethers, used in positive photoresist, is applied to a wafer using either a spray coater or a spin coating device. In either case, the spray coater places a uniform film of the photoresist on a silicon wafer. A spin coater then deposits a metered amount of resist (e.g., a glycol ether) via a closed transport system onto a 3-in or 4-in wafer, which is then spun for a specific time period to achieve a uniform 0.3- to 2-μm layer across the surface of the wafer. These operations are performed in a clean room, usually under a laminar flow hood.

The basic function of a photoresist substance is to enable the manufacturer to transfer a pattern for a circuit or other element of a semiconductor device from a mask—a glass with the pattern to be etched on the semiconductor device printed on the glass—to the semiconductor device. Ultraviolet light is directed through the mask, exposing a layer of photoresist on a silicon wafer to the pattern on the mask. The wafer is then developed, and subsequent baking, etching, and stripping processes are used to create a part of the circuit contained on the silicon wafer. A detailed description of the photoresist process has been presented by Gise and Blanchard (1986).

Glycol ether solvents based on propylene oxide have also been avail-

able for many years and are generally mixtures of two components. The major component contains a secondary hydroxyl, while the minor component has a primary hydroxyl group, but a branch structure. In contrast, the ethylene oxide-based products have a linear structure with a primary hydroxyl. The ethylene oxide-based products are generally better solvents, and consequently they have dominated the coating market (Smith, 1984). For example, when comparing the properties of 2-ME with the properties of propylene glycol monomethyl ether, the evaporation rate of the propylene oxide-based product is about twice that of the ethylene oxide-based product; the flash point is much lower, and the solution viscosity with coatings resins is very similar (Smith, 1984).

It is not always possible to match both solvent activity and the evaporation rate of an ethylene oxide-based glycol ether with a propylene oxide-based product. This is one of the reasons it is sometimes difficult to substitute ethylene oxide-based solvents in coatings systems with propylene oxide-based products. In most coatings systems, ethylene oxide-based products have better solvent activity, better coupling ability, and give better solvent release from a coating than the propylene oxide-based products (Smith, 1984). Manufacturers are currently trying to develop other types of less hazardous but effective glycol ethers (Horton and Owens, 1985; Cox, 1985).

Exposure Hazard Rating of the Glycol Ethers

Unlike so many of the common solvents used in industry, the glycol ethers enjoy a rather low vapor pressure. As shown in Table 2, the vapor pressures for the four glycol ethers discussed in this paper range in value from 1 to 10 mm Hg at 25°C (room temperature). These are markedly lower than common solvents like toluene and acetone, which have vapor pressures of 30 and 227 mm Hg, respectively, at the same temperature. The low vapor pressure of the glycol ethers, coupled with the conditions under which they are used, explains the low levels of airborne exposure that have been observed in the industrial hygiene surveys of the chip (wafer) manufacturing industry [National Institute for Occupational Safety and Health (NIOSH), 1982].

In an effort to predict which chemicals are most likely to be a concern in workplace air, industrial hygienists and ventilation engineers have found it useful to calculate the vapor hazard index (VHI) for the various chemicals used in a given process. The VHI is the vapor pressure (VP) at 25°C divided by the occupational exposure limit (VHI = VP/TLV) for that chemical (Committee on Industrial Ventilation, 1986). Although the VHI concept was devised in the 1940s, it remains a useful tool for identifying those chemicals that are likely to pose the greatest hazard in the workplace since it accounts for both volatility and toxicity/undesirability. One shortcoming is that for VHIs to be comparable, it is assumed that various chemicals are used within similar pieces of equipment and

under similar use conditions. In short, a chemical with a high vapor pressure and a low TLV will have a high VHI and, therefore, may require special effort to ensure that the airborne concentrations will not reach excessive levels. On the other hand, chemicals that have VHIs less than 1 are generally easy to control. The VHI can be based on either OSHA PELs or ACGIH TLVs. For the glycol ethers, VHIs derived from the TLV are particularly useful since the rationale for these limits considered their developmental toxicity and reproductive hazard (ACGIH, 1986).

Based solely on the volatility of these four glycol ethers, 2-methoxyethanol and 2-methoxyethanol acetate should be most difficult to control. 2-Ethoxyethanol acetate, on the other hand, should be found at the lowest airborne concentrations in the workplace, assuming that all other factors are equal (Table 2). As discussed later, the air sampling data confirm that volatility is a reasonably accurate predictor of the relative airborne concentrations for these chemicals.

POTENTIAL FOR WORKPLACE EXPOSURE

Relatively small quantities of the glycol ethers are used within a workroom at any given time during chip manufacturing. About 1–2 ml is applied to 3-in or 4-in wafer (chip) during the spinning step. One-half to two gallon bottles of photoresist are normally placed in cabinets below the equipment in which they will be used. Generally, local exhaust ventilation is used to remove any vapor that is produced. The bottles of photoresist are changed as required and the "technicians" involved in the change-out procedure wear appropriate protective gloves and an apron to prevent skin contact. The procedure involves removing the aspirator delivery tube from the spent bottle of resist and installing a fresh bottle.

The spinner heads on the coaters are cleaned periodically to remove photoresist that has adhered to the assembly over time, and this presents an opportunity for exposure. Typically, the clean-up requires the use of some type of solvent such as acetone or xylene to remove hardened resist. Cleaning operations are conducted in a cleaning station, which is equipped with a local exhaust system and drains that remove excess waste solvent. The technician involved in the cleaning operation wears appropriate protective equipment (gloves and apron) to prevent skin contact.

PERSONAL PROTECTIVE EQUIPMENT

In most semiconductor operations, personal protective equipment is required of all persons who handle the glycol ethers. Gloves are the primary protective device. On rare occasions, when concentrations are potentially in excess of 5 ppm, respirators are used. In 1981–1982, tests to evaluate the permeability of the glycol ethers through various glove ma-

terials in common use in the semiconductor industry were performed (Loreti and Nohrden, 1983). These tests showed that gloves made of nitrile and butyl rubber or neoprene provided the best protection (Table 3). These types of gloves are now the ones most frequently used in this industry.

Three kinds of respirators for preventing inhalation exposure to the glycol ethers are available for use; however, due to the low concentrations encountered, they are rarely necessary. Half masks equipped with carbon canisters are the most common type. These are used in situations where exposures are not likely to exceed 5 times the TLV, since these respirators usually only provide a protection factor of 10. Supplied-air respirators are occasionally worn by maintenance workers engaged in work or clean-up operations. When used, 15 cubic feet per minute of air is supplied to full-face masks, and this provides protection factors of at least 2000.

DEVELOPMENTAL TOXICOLOGY: BACKGROUND

Segment II studies are designed to evaluate the teratogenic potential of a test agent and they are the most common tests to evaluate prenatal toxicity. FDA segment II evaluations are performed in both a rodent and

TABLE 3. Time to Break-Through and Permeation Rates for Various Gloves and Solvents[a,b]

Solvent	Sol-Vex nitrile	Neoprene unsupported	Neox-supported neoprene	PVA-supported polyvinyl alcohol	Natural rubber
Acetonitrile	30 min (F)	30 min (VG)	1.5 h (E)	1 h (E)	4 min (VG)
2-Methoxy ethanol (2-ME)	1.5 h (VG)	1.5 h (VG)	ND (E)	10 min (G)	45 min (G)
2-Ethoxyethanol (2-EE)	3.5 h (G)	45 min (E)	4 h (E)	1.25 h (G)	45 min (G)
2-Ethoxyethanol acetate (2-EEA)	1.5 h (G)	25 min (E)	1.25 h (E)	40 min (VG)	11 min (G)
Diacetone alcohol	4 h (E)	5 h (E)	ND (E)	2 h (VG)	20 min (VG)
2-Methoxy ethanol (2-ME)	11 min (G)	25 min (G)	70 min (VG)	6 min (G)	4 min (VG)
Pyridine	—	—	—	50 min (G)	5 min (F)
1,1,1-Trichloroethane	1.5 h (P)	—	—	1 h (E)	—

[a]Based on Loreti and Nohrden (1983). From Edmont Research and Development (1986).

[b]The first number represents the permeation breakthrough time, followed by a permeation rating, which corresponds to the following:

ND, None detected during a 6-h test (equivalent to excellent).

E, Excellent; permeation rate of less than 0.15 $mg/m^2 \cdot s$.

VG, Very good; permeation rate of less than 1.5 $mg/m^2 \cdot s$.

G, Good; permeation rate of less than 15 $mg/m^2 \cdot s$.

F, Fair; permeation rate of less than 150 $mg/m^2 \cdot s$.

P, Poor; permeation rate of less than 1500 $mg/m^2 \cdot s$.

NR, Not recommended; permeation rate of greater than 1500 $mg/m^2 \cdot s$.

nonrodent species, most frequently the rat and rabbit. Males used for breeding are not administered the test agent. Typically d 0 of presumed gestation is the day spermatozoa, a vaginal plug (rats, mice), or insemination (rabbits) occurs. Animals are treated during the period of major organogenesis and cesarean-sectioned (C-sectioned) 1 or 2 d prior to the expected time of natural delivery. Treatment periods for commonly used species are rat, d 6–15 (C-section on d 20); mouse, d 6–15 (C-section on d 18); rabbit, d 6–18 (C-section on d 28–30); and hamster, d 6–14 (C-section on d 15). The segment II test protocol is a rigorous one, since the pregnant animal is exposed to the toxicant throughout the critical portions of the pregnancy (Christian, 1983).

There are four ways in which altered in utero development can be demonstrated:

1. Death of the developing organism: either embryo or placenta first and regardless of whether or not developmental abnormality may have preceded or even caused death (Johnson, 1984a).
2. Structural abnormality: generally considered as gross anatomical, though histologic and other changes are recognized with increased frequency (e.g., Christian, 1983; Kavlock, 1983).
3. In utero growth retardation (IUGR): generally (but need not necessarily be) restricted in in utero; growth retardation of about 25–30% below comparable controls.
4. Functional deficiency, e.g., decrement of anticipated postnatal capability: can include effects on numerous systems other than central nervous system, e.g., lung; most will perhaps eventually be found to have a configurational basis.

These can arise from a variety of causes (Wilson, 1973a,b). Currently, there is no internationally accepted congenital abnormality classification system, although the one developed by the World Health Organization (WHO) is quite good (WHO, 1978; Johnson and Christian, 1986). These classes of effects, however, as well as the mechanisms that cause them, have little influence on the risk-assessment process.

Three terms are often used to describe the results of developmental toxicity tests. For purposes of risk assessment, "teratogenic" should describe those chemicals that have been shown to produce structural abnormalities. "Embryotoxic" and "fetotoxic" appear to be the most ill-defined terms. Several papers have used embryotoxic as the sum of all possible toxic actions affecting the embryo, including teratogenic, embryolethal, and other effects. Black and Marks (1986) have proposed that "embryotoxicity" should describe the loss of an embryo and the term "fetotoxicity" should describe less severe effects. "Fetotoxicity" has also been used to describe the toxic or degenerative effect on fetal tissues and organs after organogenesis (Rao et al., 1981; EPA, 1986). Some authors

have suggested that fetotoxic effects are usually transient and that bones and organs would be expected to continue to develop to their normal appearance and function. However, there are examples of fetotoxicity (in humans and test animals) where the adverse effects persist throughout growth and development (e.g., phenylketonuria). Perhaps for this reason, the EPA guidelines (1986) note that the toxic effects could include malformations and variations, altered growth, and in utero death.

To predict the dose at which no health hazard should exist in humans, identification of a NOEL (no-observed-effect level) or a NOAEL (no-observed-adverse-effect level) in developmental toxicity studies is usually necessary. As presented in Table 4, from studies of substances that are known to adversely affect humans and for which there is some knowledge of the level of human exposure, it is possible to evaluate the accuracy of animal data to predict the no-effect level in humans (Nisbit and Karch, 1983). From these historical data, it is evident that the application of a rather modest safety factor to the animal NOEL (no larger than 100), has usually been sufficient to protect humans from adverse developmental effects.

It is reassuring that all human teratogens, except possibly one, have been detected in animals (Heinowen et al., 1977; Holson et al., 1981; Hemminki and Vineis, 1985). Whether they were all prospectively detected is a different consideration, although this did occur with several chemicals such as the androgens (Johnson and Christian, 1986). This issue has been clouded, at least in part, due to the fact that thalidomide was not detected in animal tests before its effects were seen in humans. However, it is important to remember that thalidomide was the driving force behind development of the contemporary safety evaluation studies that replaced the old two-litter test, which probably would not have detected the adverse effects of thalidomide. Nevertheless, accusations that thalidomide would not be identified under the currently used segment II test battery do not appear supportable. Johnson and Christian (1984)

TABLE 4. Comparison of Human and Animal Developmental Toxicity Tests[a]

Agent	*Human effect level*	Animal species *and effect level*
Alcohol	0.4–0.8 g/kg·d	Rat 1.5
Aminopterin	50 μg/kg·d	Rat 100
Diphenylhydantion	2 mg/kg·d	Mouse 50
Diethylstilbestrol	20–80 mg/kg·d	Rhesus 200
Methotrexate	42 μg/kg·d	Rat 200
Methyl Hg	0.5 μg/kg·d	Rat 250
Polychlorinated biphenyls	70 μg/kg·d	Rhesus 125
Thalidomide	0.5–1.0 mg/kg·d	Rabbit 2.5

[a]From Nisbet and Karch (1983).

have noted that the current segment II tests would almost certainly have detected a variety of structural abnormalities in rabbits and, in all likelihood, rats would have shown greater resorptions rather than an increased incidence of abnormalities; either would have been sufficient to prevent its approval. Further, the A/D ratio for thalidomide is about 20; a figure that would certainly have demanded special attention.

HAZARD ASSESSMENT

A good deal of the confusion in developmental toxicity has been caused by the lack of distinction between toxicity, hazard and risk estimation. Toxicity is a property of a chemical like its flammability. In contrast, hazard is the ability of the test chemical, under a given set of conditions, to cause a specific kind of adverse effect (i.e., developmental toxicity, neurotoxicity, cardiotoxicity). Tests for developmental toxicity identify those chemicals that might pose a "hazard" to the developing fetus. On the other hand, the risk posed by a chemical is the probability or likelihood that an adverse outcome will occur in a group that is exposed to a particular concentration or dose. Risk, therefore, is generally a function of exposure.

One of the parameters in the hazard assessment of developmental toxins is the relationship between the lowest dose that produces signs of overt toxicity in adults (*A*) and the lowest dose that produces any one of the three signs of developmental toxicity in the offspring (*D*). Fabro et al. (1985) suggested that the ratio of the LD05 in the mother compared to the dose that did not affect embryonal development, which they called the "relative teratogenic index," might be a useful index for identifying chemicals likely to be hazardous to humans. Regrettably, this approach has been found to have numerous shortcomings and has therefore received limited attention.

The usefulness of the A/D relationship is illustrated in Fig. 2. Most agents tend to affect both the mother and the conceptus at approximately the same general dosage level (Johnson and Christian, 1986). These are known as coaffective agents, i.e., they have a low hazard index, and they tend not to exhibit developmental selectivity ($A/D < 1$). For these chemicals, there is risk of developmental toxicity only if maternally toxic doses are approached or exceeded—a situation that should not occur if occupational exposure limits such as TLVs are met (Johnson, 1987). On the other hand, some agents can alter some aspect of development at a small fraction of the adult toxic dose, and these can present a genuine developmental hazard ($A/D > 1$). For these, there is a genuine risk of adverse effects on development at exposure levels that are innocuous to adults.

The A/D relationship, however, is only one of many considerations in assessing the developmental hazard. For example, consideration must be

given to these chemicals where A/D varies between species. In addition, the A/D ratio is unable to reflect the differences in the severity of the adverse effects observed in the mother (e.g., weight loss) versus those observed in the offspring (e.g., gross deformity). The slope of the dose-response curve is also not reflected in this approach. Nonetheless, our experience to date suggests that chemicals that are likely to pose a significant risk to pregnant workers will usually meet two criteria. First, exposure (uptake) will be greater than 1/100th the animal NOEL. Second, the adverse effect on development can occur at doses that do not produce toxic effects in the adult (e.g., high A/D ratio) (Johnson, 1984).

Comparative Metabolism

When assessing the developmental effects of any chemical, it is useful to understand its metabolism in animals and, if possible, in humans. In 1983, Miller et al. (1983a, 1985) noted that little is known about the metabolism of 2-ME or the other glycol ethers except that ethylene glycol monobutyl ether (2-BE), a structural homolog of 2-ME, was apparently oxidized to *n*-butoxyacetic acid in the rat, rabbit, guinea pig, dog, monkey, and human (Carpenter et al., 1956). Jonsson and Steen (1978) have confirmed *n*-butoxyacetic acid as a urinary metabolite of 2-BE in rats. Hutson and Pickering (1971) have studied the metabolism of another structural homolog of 2-ME, ethylene glycol isopropyl ether (EGiPE), in rats. They showed that following an ip injection of [^{14}C]EGiPE, the major routes of excretion were urine (73%) and expired air (14%). Isopropoxyacetic acid and its glycine conjugate were identified as the two major urinary metabolites of EGiPE.

Based on results obtained with these close structural homologs of 2-ME, together with the fact that 2-ME is a substrate for human and equine alcohol dehydrogenase in vitro (Tsai, 1968; Blair and Vallee, 1966), Miller et al. (1983a) it was expected that 2-ME might be oxidized to methoxyacetaldehyde via alcohol dehydrogenase (ADH) and then further oxidized to methoxyacetic acid via aldehyde dehydrogenase (Fig. 1). In the study (Miller et al., 1983a) male Fischer 344 rats were given a single po dose of approximately 1 or 8.7 mmol/kg of [^{14}C]EGME (ethylene glycol monomethyl ether). Approximately 50–60% of the administered ^{14}C was excreted in urine, and about 12% was eliminated as $^{14}CO_2$ within 48 h after a single po dose of [^{14}C]EGME. Methoxyacetic acid was identified as the primary urinary metabolite of EGME, which accounted for 80–90% of the total ^{14}C in urine. Since methoxyacetic acid has been shown to produce the same spectrum of toxicity as 2-ME in male rats, it is likely that the adverse effects of EGME are the result of its in vivo bioactivation to methoxyacetic acid. Hence, Miller and co-workers (1983a, 1984) concluded that the differences of metabolites appeared to be the underlying basis for the remarkably different toxicologic properties of 2-ME and propylene glycol monomethyl ether, PGME. Foster et al. (1984) have sug-

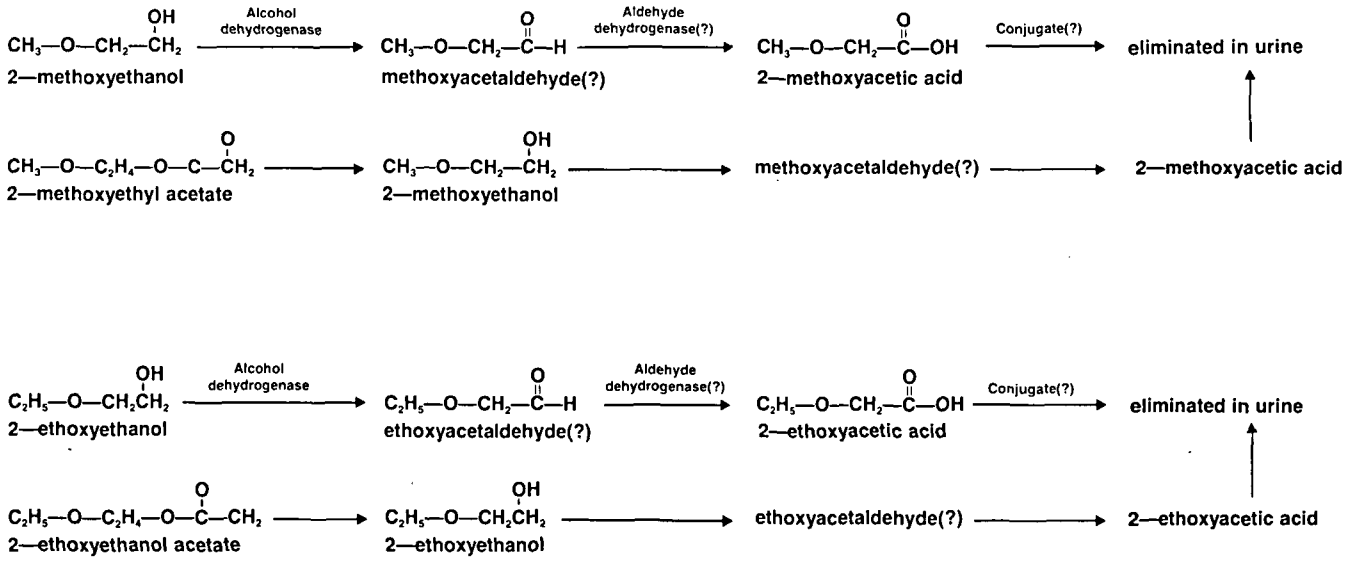

FIGURE 1. The likely metabolism of 2-ME, 2-MEA, 2-EE, and 2-EEA. The formation of methoxyacetaldehyde and ethoxyacetaldehyde, with subsequent conversion to methoxyacetic acid and ethoxyacetic acid, respectively, has been suggested but the evidence is not convincing. The methoxyacetic acid (MAA) and ethoxyacetic acid (EAA) are generally considered the chemicals responsible for causing the developmental effects.

gested that methoxyacetaldehyde might be formed prior to the methoxyacetic acid and that the former could be the toxic species (Fig. 1). However, other studies have not indicated that the acetaldehyde is the proximate teratogen. Work by Brown and co-workers (1984) and Ritter and co-workers (1985) confirmed that methoxyacetic acid is the likely proximate teratogen for both 2-ME and di(2-methoxyethyl)phalate (DMEP). Yonemoto et al. (1984) also showed adverse effects of 2-methoxyacetic acid on rat embryos in culture.

The metabolism of 2-ME appears to be similar among several species. For example, a close structural homolog of 2-ME, ethylene glycol monobutyl ether (2-BE), is oxidized to *n*-butoxyacetic acid in a variety of species: rat, rabbit, guinea pig, dog, monkey, and human (Carpenter et al., 1956). In addition, this has been confirmed in rats by Jonsson and Steen (1978). Their evidence plus the Miller et al. (1983a, 1984) studies provides confidence regarding cross-species consistency of metabolism (i.e., there are likely to be few major differences in the metabolism of this type of compound across several species). Recent work by NIOSH indicates that ethoxyacetic acid in the urine of workers might be an appropriate indicator of exposure (NIOSH, 1986; Smallwood et al., 1987).

By analogy, it is likely that the acetates of 2-methoxyethanol and 2-ethoxyethanol are metabolized via hydrolysis to the parent molecules, 2-ME and 2-EE, respectively (ACGIH, 1986). In support of this postulate, it has been noted that on an equimolar basis, the respective acetate esters were about as potent as 2-ME and 2-EE in producing testicular effects and leukopenia in exposed animals (Nagano et al., 1979; ACGIH, 1986; Johnson, 1984). The available data strongly suggest that 2-ME and 2-EE are metabolized to methoxyacetic acid and ethoxyacetic acid, respectively (Fig. 2).

Mutagenicity

McGregor (1984) subjected 2-ME to the following assays for genetic toxicity: the Ames test, unscheduled DNA synthesis (UDS) assay in human embryo fibroblasts, sex-linked recessive lethal (SLRL) test in *Drosophila*, dominant lethal test in male rats, bone-marrow metaphase analysis in male and female rats, and the sperm abnormality test in mice. In vivo test animals were exposed to atmospheric concentrations of 25 or 500 ppm 2-ME. Point mutations in the Ames test and UDS in fibroblasts were not increased, while the SLRL test gave ambiguous results that the authors believed to warrant further investigation. Chromosomal aberration frequencies were not increased in rat bone marrow, but there was evidence from the dominant lethal tests that 2-ME had profound effects on male rat fertility during the meiotic phase. Pregnancy frequency was greatly reduced and preimplantation losses were large. There was also evidence of postimplantation losses. Sperm abnormalities were slightly increased in the mice. These effects on male reproductive cells were

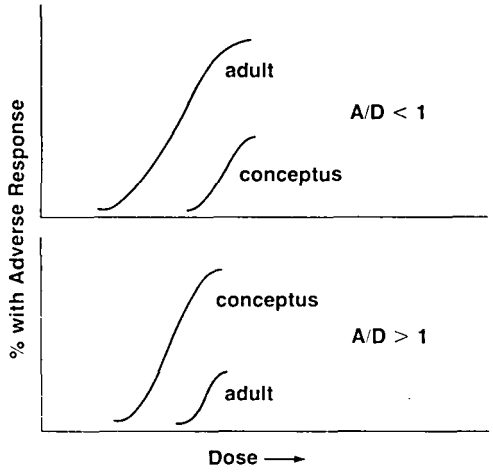

FIGURE 2. The relationship between adult and developmental effective doses. In the plot where A/D is less than one, toxic effects are seen in the pregnant animal at doses lower than those which adversely affect the conceptus. In contrast, where the A/D ratio is greater than one, the conceptus is much more sensitive to the effects of the chemical than the mother (Based on Johnson, 1986).

seen only at 500 ppm. The likely teratogen, the 2-methoxyacetic acid metabolite of 2-ME, was not tested for mutagenicity, and its formation is unlikely even in the activated portion of the Ames test battery. The authors concluded that 2-ME lacked genotoxic potential but, due particularly to its effects on fertility, all data needed to be considered in any safety evaluation of this chemical.

DEVELOPMENTAL AND REPRODUCTIVE TOXICOLOGY TESTS

2-Methoxyethanol (2-ME)

2-ME has been studied in numerous animal species (rats, rabbits, and mice) in recent years (Nagano et al., 1981; Hanley et al., 1982a; Miller et al., 1982b, 1983b; Horton et al., 1985). Standard segment II developmental toxicity studies were conducted via inhalation, the typical route of human exposure in industry. These data should provide a sufficient understanding of the dose-response relationship and the NOEL for predicting the hazard and risk to exposed humans.

Hanley et al., (1982a) exposed pregnant CF1 mice to 2-ME for 6 h/d from d 6 to 15 of gestation at concentrations of 0, 10, and 50 ppm. The pregnant dams were autopsied on d 18 according to the standard segment II protocol. At the highest dose level (50 ppm), there was a minimal depression of maternal weight gain during the treatment period along with some minimal changes in white blood cell and platelet counts. Consequently, slight toxicity was observed in the mother at 50 ppm. At this same high dose, but not at 10 ppm, there were adverse effects on prena-

tal development. The number of fetuses per litter was reduced significantly at 50 ppm, and the number of resorbed implantation sites was increased, as was the percent of litters with resorptions. The skeletal variations, both in sternebrae as well as in incidence of lumbar ribs, were increased also at 50 ppm. Unilateral testicular hypoplasia and hemorrhage in the male fetuses were also reported at this dose level (Johnson, 1984). In this and some of the other studies of the ethylene glycol ethers, the apparent difference in maternal body weight gain might have been lost if maternal weight had been corrected for the weight of uterine content.

Nagano et al. (1981) reported a segment II study performed in pregnant ICR mice treated by intragastric intubation of 2-ME. Doses were 0, 31.25, 62.5, 125, 250, 500, or 1000, mg/kg maternal body weight. Maternal body weight gain was depressed at doses of 125 mg/kg and above. This may have been due to the reduction in litter size. At both this dose and 31.25 mg/kg·d, there was a slight increase in the number of skeletal variations but there were no frank malformations. Syndactyly, polydactyly, etc. did not occur at an elevated rate below the dose also capable of interfering with maternal weight gain (125 mg/kg·d). No clear NOEL was identified in this study.

Hanley and co-workers (1982b) exposed pregnant rats to 0, 3, 10, and 50 ppm of 2-ME. Exposure to 50 ppm reduced maternal weight gain very slightly at the onset of treatment and depressed a series of hematologic parameters in a concentration-related manner. The conceptus also showed delayed ossification patterns and rib spurs at 50 ppm. In another study using rabbits, where the doses were also 0, 3, 10 and 50 ppm, the high-dose group (50 ppm) had markedly depressed maternal weight gain from d 6 through 14 and significantly increased absolute liver weight. Examination of the fetal rabbits showed that resorptions were increased at the high dose, whereas fetal body weight and skeletal maturation were both reduced. In addition, structural abnormalities were seen at the high dose in association with a marked effect on maternal weight gain. Rabbits exposed to 10 ppm had a statistically significant increase in the percent of implantations undergoing resorption when compared to concurrent controls; however, as discussed by Johnson (1984), this result was not biologically significant, as the study authors concluded, because the statistics are more a function of the low incidence of resorptions in the concurrent controls, i.e., 4% on a per implantation basis. The resorption rate observed in the 10 ppm exposed groups was well within the historic control range for rabbits in this laboratory. This interpretation has been questioned since concurrent controls usually carry more weight than historical controls, especially if the animals were randomly selected (EPA, 1984).

In a complex study conducted by Miller et al. (1983b), adult rats and rabbits were exposed via inhalation for 13 wk to 2-ME at concentrations of 0, 30, 100, and 300 ppm. In each test species, both absolute and rela-

tive testes weights were reduced at the high dose. In the rabbits, there was a reduction of testes weight at the 100-ppm level, while at both the 100- and 300-ppm levels reduced body weight gain was evident in both rats and rabbits. It should be noted, however, that rabbit weights can fluctuate randomly irrespective of treatment effects. Also observed was a concentration-related reduction in numbers of platelets. When the 13-wk inhalation study was repeated with just male rabbits at doses of 0, 3, 10, or 30 ppm, there were no adverse effects due to treatment (Miller et al., 1983b). From these studies, an experimental NOEL of 30 ppm for testicular effects was clearly identified for both species (Johnson, 1984).

Horton et al. (1985) have evaluated the phase-specific and dose-related teratogenic effects of 2-ME in CD1 mice following oral administration. They showed that 2-ME (EGME) was not toxic to the adult female after multiple doses of 250 mg/kg or a single administration of 500 mg/kg; however, 2-ME produced fetal weight loss and increased resorptions at 500 mg/kg. The malformations were specifically related to the development stage at the time of exposure. The no-observed-effect dose for the induction of digit malformations after a single administration of 2-ME was 100 mg/kg. At 175 mg/kg, digit anomalies were induced without any concurrent reduction in fetal body weights.

Horton et al. (1985) suggested that the *A/D* ratio for the mouse may be at least 6.0. However, as discussed by Johnson (1988), the A/D in this study would almost certainly have been less than 5 had the animals been dosed throughout their pregnancy since the test protocol didn't give the mothers adequate time to elicit the toxic effects.

Reproductive Toxicity of 2-ME

A number of studies to evaluate the reproductive hazard of 2-ME have been conducted (see Table 6). Nagano et al. (1979) orally dosed JCL-ICR mice with 2-ME at levels of 62.5, 125, 250, 500, 1000, 2000, and 4000 mg/kg·d for 5 d/wk for 5 wk and evaluated them for testicular atrophy. The no-effect level for testis weight was 125 mg/kg·d.

In a less comprehensive study, Samuels et al. (1984) exposed rats to a single saturated vapor of 2-ME and subsequently studied the effects on the testis. There were marked reductions in testicular weight 14 d after exposure to 2-ME. In a follow-up study, designed to establish the effect of a single exposure to 2-ME, mature male albino rats were exposed to various concentrations for a single 4-h period and sacrificed 14 d later. Following this single exposure, an exposure-related decrease in testis weight was observed in rats exposed to 5000, 2000, or 1250 ppm. Histopathological examination revealed disordered spermatogenesis and tubular atrophy in these animals. Minimal degenerative changes were seen in the testis of rats exposed to 625 ppm 2-ME. Testicular weights were reduced in rats examined 2 d after exposure to 2500 and 1000 ppm 2-ME and remained depressed when compared with control values for up to

19 d following exposure. Histopathological examination of the testes revealed disordered spermatogenesis in these animals.

Perhaps the most elaborate evaluation of the reproductive toxicity of 2-ME has been conducted by Rao et al. (1983). They conducted a dominant lethal study in rats where either the adult males or adult females were treated by the inhalation route for 13 wk at vapor concentrations of 0, 30, 100, or 300 ppm and were then bred to untreated partners. At the highest exposure level, male fertility was depressed, but no effect on this parameter was seen at 100 ppm. Parental hematology and testes weight were affected at 300 ppm even 11 wk postexposure. In marked contrast, there were no effects at 11 wk following exposures of 30 and 100 ppm.

In a similar study, Foster et al. (1983) dosed rats po with 50–500 mg/kg·d of 2-ME and 250–1000 mg/kg·d of 2-EE for 11 d. Testicular damage following 2-ME treatment was observed 24 h after a single dose of 100 mg/kg. At 16 h after a single dose of 500 mg/kg, mitochondrial damage in the spermatocytes was one of the first subcellular changes to demonstrate similar toxicity. Animals treated with 2-EE developed a similar lesion to that produced by 2-ME; however, to obtain damage of equivalent severity, a larger dosage for a longer period was required. In limited studies, 2-methoxy- and 2-ethoxyacetic acids used at doses equimolar to their parent compounds (500 mg/kg of 2-ME or 2-EE for 4 or 11 d, respectively) produced lesions of equivalent severity to the corresponding glycol ether. These data represent good evidence that 2-methoxyacetic acid and 2-ethoxyacetic acid are the likely metabolites and that they are responsible for the toxic effects. Following administration of 500 mg/kg·d of 2-ME for 4 d, the testes recovered weight, and the majority of tubules recovered their spermatogenic potential within one full maturation cycle. No-effect levels for the 11-d treatment period were 50 and 250 mg/kg·d for 2-ME and 2-EE, respectively.

Chapin and Lamb (1984) studied the histologic effects of 2-ME on the spermatocytes of Fischer 344 rats. Adult male Fischer 344 rats of proven fertility were dosed po with 0, 50, 100, or 200 mg/kg·d of 2-ME for 5 d. Each male was then mated with 2 females/w for 8 wk. They found that the fertility of males treated with 200 mg/kg·d declined at wk 4, and remained low for the rest of the study. There was a modest but significant increase in the number of resorption sites at wk 5 and 6 in the high-dose group. A decrease in the number of litters observed at wk 5 after dosing in the 100-mg/kg·d group was also observed. There were time- and dose-related decreases in sperm concentrations and motility, primarily in the 100- and 200-mg/kg·d groups, as well as concurrent elevations in the number of abnormal sperm forms in the epididymis. These studies showed that 2-ME was a very weak inducer of dominant-lethal mutations, and produced effects on late-stage spermatids and spermatogonia.

The bulk of data on the reproductive toxicology of 2-ME indicate that,

in rats and rabbits, the adult NOEL is greater than 10 ppm and that the NOEL for developmental effects on the embryo is virtually the same. In addition, mice treated by the most likely route of human exposure, inhalation, had NOELs similar to those in rats and rabbits. Based on these data, in calculations associated with this assessment, a NOEL of 10 ppm will be considered the dose at which no adverse effects (NOEL) have been seen in animal tests.

2-Methoxyethanol Acetate (2-MEA)

The developmental toxicity of the acetates of the methoxy and ethoxy glycol ethers have not been evaluated as thoroughly as 2-ME and 2-EE, primarily because the apparent metabolic pathway for 2-MEA and 2-EEA has been expected to form the parent molecules and then the proximate teratogen. As a result, the acetates are expected to present a developmental hazard similar to the parent molecules.

Nagano et al. (1979) studied 2-MEA to evaluate its testicular toxicity and to assess whether the effects and potency were similar to 2-ME. In this study, groups of mice were dosed orally 5 d/wk for 5 wk with 500 mg/kg of 2-ME, 500 mg/kg of 2-MEA, 2000 mg/kg of 2-EE, and 4000 mg/kg of 2-EEA. Approximately equal degrees of atrophy were produced from exposure to these doses, and each produced leukopenia. On an equimolar basis, the respective acetate esters were about as potent as 2-methoxyethanol and 2-ethoxyethanol in producing testicular effects and leukopenia (Nagano et al., 1979; ACGIH, 1986).

Based on the reported testicular effects and the likely hydrolysis of 2-MEA to 2-ME, the NOEL for developmental effects for 2-ME seems to be an appropriate estimate of the NOEL for 2-MEA. Both chemicals should be considered developmental and reproductive toxins in animals. Since a NOEL of 10 ppm has been identified for 2-ME, a NOEL of 10 ppm for 2-MEA seems appropriate for risk-assessment calculations. Based on the available data, the ACGIH TLV Committee proposed that the TLV for 2-MEA be lowered from 25 to 5 ppm, and this was formally accepted in 1984. This figure provides only a twofold safety factor below the animal NOEL.

2-Ethoxyethanol (2-EE)

Ethylene glycol monoethyl ether (2-EE) has also been studied according to the standard segment II developmental toxicity protocols via inhalation. Tinston et al. (1983a) exposed Wistar rats to 2-EE vapor for 6 h/d on d 6–15 of gestation at levels of 0, 10, 50, and 250 ppm. In this study, which was reviewed by Johnson (1984), an unusually large number of endpoint assays were conducted. For instance, patterns and degrees of ossification were reported not just for vertebrae but for vertebrae at specific vertebral levels analyzed for portions of individual vertebrae, i.e., centrum, arch (pedicle and lamina), and transverse processes (both left and right). Johnson noted that when so many parameters are examined, it

can be expected that there will be instances of statistical differences occuring between groups that may not be biologically significant. Careful examination of the data regarding all endpoints (e.g., implantations, resorptions, litters, external viscera and hard tissue status) showed marked effects at 250 ppm. In addition, at this dose there were slight effects on the maternal animal evidenced as a reduction in hemoglobin (g/dl) and on hematocrit. The conceptus tended to be smaller and to have increased numbers of skeletal variations. No adverse effects on any aspect of maternal or developmental biology were observed at 50 ppm or below.

The incidence of preimplantation loss at 10 and 50 ppm observed by Tinston and co-workers (1983a) should not be considered treatment-related (Johnson, 1984). Two reasons support this conclusion: first, no consistent dose-response relationship was found (2.4% in controls, and 9.7%, 14.3%, and 6.2% in 10, 50, and 250 ppm groups, respectively). Second, concurrent control incidence was well below the historical control rate in this laboratory, where implantation loss in controls in 10 other studies ranged from about 4 to 13% (Johnson, 1984).

An elaborate study of 2-EE has been conducted in both rats and rabbits by Andrews et al. (1981). Rats were exposed to 765 ppm or 202 ppm of 2-EE vapor for 3 wk before mating and then from d 1 through 19 of pregnancy. No significant effects were produced in the adult rats at 202 ppm, although marked toxicity was evident at 765 ppm. At 202 ppm, suppressed pup weight and an increased incidence of a variety of skeletal variations and developmental delays were observed. The same study was repeated in rabbits, whereas they were exposed from d 1 through 19 of pregnancy at levels of 0, 160, and 617 ppm, 7 d/wk and 7 h/d. The high dose of 617 ppm was severely toxic to the dams and markedly depressed maternal weight gain during pregnancy. At 160 ppm, this effect was less obvious but may be dose-related. From these studies, the researchers did not identify a NOEL for either rats or rabbits.

In an attempt to identify a NOEL in rabbits (Dutch belted), Tinston et al. (1983b) conducted a standard segment II study. Pregnant females were exposed to 2-EE by inhalation at levels of 0, 10, 50, and 175 ppm increased the number of skeletal variations and minor abnormalities in the concepti, but did not adversely affect maternal body weight or a variety of other adult toxicity endpoint parameters. At both 10 and 50 ppm, 2-EE did not adversely affect implantation, resorption, or soft or hard tissue when measured in these rabbit fetuses (Johnson, 1984).

The studies by Tinston et al. (1983a,b,d,e) and Andrews et al. (1981) of 2-EE suggest that 50 ppm is a likely NOEL for the fetus. In addition, it appears that 50 ppm is a no-effect level for developmental toxicity in two species (rat and rabbit) exposed by the route most relevant to humans. Comparing the available studies, it is clear that 2-EE is less potent than is 2-ME with respect to its developmental toxicity. In view of the consist-

ency between studies and species, the criteria usually applied in selecting the size of a safety factor (Dourson and Stara, 1983; Dourson, 1986; Weil, 1972), and considering the results of testing involving similar glycol ethers (2-ME and 2-MEA), a safety factor less than 100 can be applied to this NOEL to estimate acceptable limits of exposure for humans. In light of its favorable use in industry and these data, in 1982 the ACGIH TLV Committee set the TLV for 2-EE at 5 ppm (about 10-fold less than the animal NOEL).

2-Ethoxyethyl Acetate (2-EEA)

The National Institute for Occupational Safety and Health (NIOSH) has conducted some developmental toxicology studies on 2-EEA. Sprague-Dawley rats were exposed to 2-EEA by inhalation for 7 h/d from d 7 through 15 of gestation using a segment II protocol (Nelson et al., 1982). The maternal animal data are not available for analysis, but the authors stated that maternal animals showed no overt toxicity. At concentrations of 594, 390, and 130 ppm, no adverse effects were noted in the mother; however, at 594 and 390 ppm there were adverse effects on the embryo. The incidence of adverse effects was only minimally elevated at 130 ppm, indicating that this dose was at, or very near, the developmental NOEL for rats (Johnson, 1984).

A state-of-the art teratology study of 2-EEA has also been reported by Tinston et al. (1983c). Pregnant Dutch belted rabbits were exposed to 0, 25, 100, or 400 ppm 2-EEA for 6 h/d on d 6–10 of pregnancy and sacrificed on d 29, at which point fetal evaluations were conducted. In addition to the usual toxicologic endpoint assays characteristic of a segment II type of developmental toxicity test, numerous maternal hematologic assays were also reported (Johnson, 1984). Toxicity in the adult rabbits was observed at 400 ppm. Both maternal food intake and weight gain during treatment were significantly reduced. Similarly, hemoglobin (g/dl) in maternal blood was significantly reduced in the 400-ppm group. Exposure to 100 or 25 ppm did not affect pregnant females beyond body weight effects during d 6–18: effects that are possibly associated with reduced feed intake (Johnson, 1984). The rabbit fetuses from mothers exposed to the maternally toxic concentration of 400 ppm showed significantly increased incidences of developmental variations as well as major and minor defects of both soft and hard tissues. In some assays, i.e., fetal weights and skeletal development, offspring whose mothers were exposed to 100 ppm may also have been adversely affected to a minor extent. Exposure to 25 ppm produced no adverse effect of any type on embryonic or fetal development. Therefore, for this study a NOEL of 25 ppm was identified in rabbits.

Recently, Tyl et al. (1987) studied 2-EEA and found that inhalation exposure of pregnant New Zealand white rabbits during organogenesis resulted in maternal toxicity at 100–300 ppm, embryotoxicity at 200 and

300 ppm, and fetotoxicity at 100–300 ppm. Significant increases in malformations were observed at 200 and 300 ppm. Exposure of pregnant Fischer 344 rats to EEA during organogenesis resulted in maternal toxicity at 100–300 ppm, embryotoxicity at 300 ppm, and fetotoxicity at 100–300 ppm. Significant increases in malformations were seen at 200 and 300 ppm. Importantly, they noted that exposure concentrations that produced embryofetal toxicity (including teratogenicity) also resulted in maternal toxicity in both species; thus the *A/D* ratio was close to unity. Exposure of rabbits and rats to 50 ppm resulted in no maternal, embryonic, or fetal toxicity and no increased incidence of malformations or variations—i.e., 50 ppm is the "no-observable effect level" (NOEL).

In light of the results of these three studies, a NOEL of 50–100 ppm has been identified for the adult rabbits (*A*), and exposures of 25–50 ppm produced no adverse effects on the offspring (*D*). Based on these data, the developmental toxicity of 2-EEA is somewhat less than that of the parent molecule (2-EE). The lesser potency of 2-EEA was acknowledged by the ACGIH TLV Committee (ACGIH, 1986) when it was noted that "On an equimolar basis, the respective acetate esters were about as potent as 2-methoxyethanol and 2-ethoxyethanol in producing testicular effects and leukopenia." This observation is consistent with the likely metabolism of the acetates and the results of toxicity tests of 2-MEA and 2-EEA.

Adequacy of the TLVs

Table 5 summarizes the toxicity data that have been gathered on these glycol ethers and presents the *A/D* ratios. Johnson (1987) has observed that, in general, most chemicals that have been tested have *A/D* ratios near unity.

The studies of Hanley et al. (1982a,b) indicate that 2-ME could present a moderate to significant developmental hazard to humans, since it has an *A/D* ratio of 1 in rabbits and approximately 5 in mice and rats. As noted previously, the data of Horton et al. (1985) indicated that the *A/D* ratio for 2-ME in the mouse was about 6.0; however, the *A/D* ratio would almost certainly have been less than 5 had the animals been dosed throughout their pregnancy, since this test protocol did not give adequate time for the mothers to respond. This example is important since it illustrates that for the *A/D* ratio to be useful, the conditions of the segment II study must be used or the results will not be comparable; between studies (Johnson, 1988). Since 2-MEA is metabolized to 2-ME (in vivo), it will be assumed that the A/D for 2-MEA is also between 1 and 5. Based on the available data, the current TLV of 5 ppm for 2-ME and 2-MEA appears to contain a small margin of safety against developmental effects, since it is only twofold lower than its NOEL for developmental effects. A TLV in the range of 1–2 ppm, about 5- to 10-fold lower than the animal NOEL, would be more appropriate. This is consistent with the recommendation of Hart et al. (1987).

TABLE 5. Summary of Developmental Toxicity Data on Selected Glycol Ethers

Chemical	Maternal NOEL[a] (*A*)	Developmental NOEL (*D*)	*A/D*[b]	Reference
2-Methoxyethanol (2-ME)	50 ppm (mice)	10 ppm	5	Hanley et al. (1982a)
	50 ppm (rats)	10 ppm	5	Hanley et al. (1982b)
	10 ppm (rabbits)	10 ppm	1	Hanley et al. (1982b)
	125 mg/kg·d (mice)	n.d.[c]	—	Nagano et al. (1981)
2-Methoxyethanol acetate (2-MEA)		Considered analogous to 2-methoxyethanol		
2-Ethoxyethanol (2-EE)	250 ppm (rats)	50 ppm	5	Tinston et al. (1983a)
	202 ppm (rats)	n.d.	—	Andrews et al. (1981)
	160 ppm (rabbits)	n.d.	—	Andrews et al. (1981)
	175 ppm (rabbits)	50 ppm	3.5	Tinston et al. (1983b)
2-Ethoxyethanol acetate (2-EEA)	594 ppm (rats)	130 ppm	4	Nelson et al. (1982)
	100 ppm (rabbits)	25 ppm	4	Tinston (1983c)
	50 ppm (rats)	50 ppm (rats)	1	Tyl et al. (1987)
	50 ppm (rabbits)	50 ppm (rabbits)	1	Tyl et al. (1987)

[a]NOEL, no-observed-effect level (dose to which animals were exposed that does not elicit an adverse effect).
[b]*A/D*, the ratio of the dose at which no effects were seen in the adult mother divided by the dose at which no developmental effects were seen in the offspring (*D*); the larger the ratio, the greater the hazard to offspring. The *A/D* ratio can also be based on the lowest doses capable of producing overt toxicity in the adults and the lowest dose capable of producing any one of the three signs of developmental toxicity observed in a segment II evaluation.
[c]n.d., none determined.

Table 6 lists the results of tests that evaluated the reproductive potential of 2-ME. The data indicate that the NOEL for adverse reproductive outcome for 2-ME is about 30 ppm in the three species tested. In light of the six-fold margin of safety, it can be expected that as long as exposures are controlled to levels below the current ACGIH TLV (5 ppm), no adverse effects on reproductive potential would be expected to occur in workers. However, in light of its potential effect on semen, the larger margin of safety afforded by a TLV of 1 or 2 ppm seems advisable.

Tinston et al. (1983a,b) and Andrews et al. (1981) identified a maternal NOEL of 200 ppm for 2-EE, while the NOEL for developmental effects in offspring was 50 ppm. The resulting *A/D* ratio of 4 categorizes 2-EE as a chemical posing a moderate developmental hazard to humans (Johnson, 1987). Since the current TLV of 5 ppm for 2-EE is 10-fold less than the NOEL for developmental effects in test animals, this uncertainty factor appears to be minimal or inadequate, especially since dermal uptake must be negligible if the intended margin of safety is to be realized.

The hazard posed by exposure to 2-EEA is similar in magnitude to that of 2-EE. Although it is not stated explicitly, Nelson et al. (1982) apparently found no toxicity in female rats exposed to concentrations up to 594 ppm. Based on information in their study and the study by Tinston et

al. (1983c), it appears that no effects on development were observed in offspring following exposures to 100 ppm. Thus, the data suggest that 2-EEA has an *A/D* ratio of about 5. The current TLV of 5 ppm is 20-fold less than the animal NOEL; consequently, even though it has a moderate *A/D* ratio, the TLV seems appropriate.

Occupational Exposure

The Semiconductor Industry Association (SIA), a trade organization, conducted an industry-wide survey of industrial hygiene air sampling data during 1984–1985 in an attempt to describe the typical levels of exposure to several of the glycol ethers and their derivatives (Fig. 3). A total of 277 samples of workplace air were provided by seven member companies. It was estimated that these data represent about 60% of all the industrial hygiene data (personal samples) on these chemicals that have been collected by member firms. Based on discussions with industrial hygienists from member companies, these sampling data appear to be representative of the industry. The National Institute for Occupational Safety and Health (NIOSH) also conducted a study of the semiconductor industry in 1982 and the results of their 92 industrial hygiene samples, collected as part of their Health hazard Evaluation Program, were found to be comparable to those collected by the firms and are included in this assessment (NIOSH, 1982). In short, the data used to estimate employee exposure to these glycol ethers (both personal and area sampling) were based on a total of almost 400 air samples.

Sampling and Analytical Methods

In workplace air monitoring studies of this industry, NIOSH methods S361 and S79 were used to collect and identify 2-ME/2-MEA and 2-EE/2-EEA, respectively (NIOSH, 1984). The methodology involves drawing air through a charcoal tube (100 mg/50 mg) at a flow rate of 0.1 to 0.2 l/min. The glycol ethers were adsorbed on the coconut-based activated charcoal granules. Following collection, the glycol ethers were eluted (de-

TABLE 6. Summary of Reproductive Toxicity Data on 2-Methoxyethanol

Species	Lowest dose that affected reproductive tract	NOEL for reproductive effects	Adverse effect observed	Reference
Mice	250 mg/kg·d	125 mg/kg·d	Testicular atrophy	Nagano et al. (1979)
Rabbits	100 ppm	30 ppm	Reproduction	Miller et al. (1982a)
Rats	100 ppm	30 ppm	Reproduction	Miller et al. (1982a)
Rats	300 ppm	100 ppm	Dominant lethal	Rao et al. (1983)
Rats	1000 ppm	<625 ppm	Altered spermatogenesis	Samuels et al. (1984)
Rats	500 mg/kg	250 mg/kg	Damages spermatocytes	Foster et al. (1983)
Rats	100 mg/kg·d	50 mg/kg·d	Dominant lethal and sperm	Chapin et al. (1985)

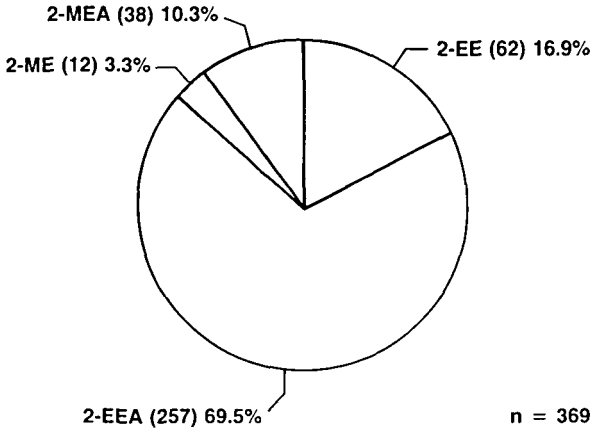

FIGURE 3. Distribution of industrial hygiene air sampling data collected among seven different firms in the semiconductor industry (1982-1985). Samples were assayed for 2-methoxyethanol (2-ME), 2-methoxyethanol acetate (2-MEA), 2-ethoxyethanol (2-EE), and 2-ethoxyethanol acetate (2-EEA).

sorbed) with a solution of 5% methanol in methylene chloride. Samples were allowed to sit for 30 min prior to removal of an aliquot for subsequent analysis. The desorption efficiency was about 90%. A 5-μl sample was injected into a gas chromatograph equipped with a flame ionization detector. Various chromatographic columns are suitable for this analysis. A 10-ft stainless-steel column with 1/8-in ID containing 10% FFAP on 80/100 mesh, acid-washed DMCS Chromosorb W, or a 20-ft stainless-steel column containing 10% FFAP on 100/120 mesh Supelcoport has been recommended. The limit of detection for most of the analyses in this study was generally 0.05 ppm. The range for the analysis was 44–160 mg/m^3.

Discussion of Workplace Exposure Data

Figure 3 illustrates the distribution of industrial hygiene air sampling data for the four glycol ethers. Of the 369 samples, 70% were for 2-ethoxyethanol acetate (2-EEA). Only 20% of the samples contained detectable levels of the glycol ethers (limit of detection was 0.5 ppm). Of the 74 samples containing detectable amounts, only 4 (5.4%) were in excess of 1 ppm. The 4 samples in excess of 1 ppm contained 2-EEA. Occupational exposure data such as these are best described by the log-normal distribution; accordingly, the statistical analysis of these data were handled in this manner (Rappaport and Selvin, 1987). It is important to note that throughout the statistical analysis of the exposure data, the limit of detection of the assay (rather than zero) was used in those instances where no detectable quality was measured. As a result, the calculated margins of safety are actually greater than shown.

Table 7 provides details concerning the type of air samples collected. Of the 371 total samples 195 (53%) were either area samples or other than

TABLE 7. Distribution of Industrial Hygiene Samples by Chemical and Type of Sampling Scheme

Chemical	Number of BZ[a] samples of operators	Number of BZ[a] samples of Technicians	Number of "other"/area samples	Total
2-EE	30	5	27	62
2-EEA	90	26	141	257
2-ME	6	1	5	12
2-MEA	14	3	21	38
Total	140	35	194	369

[a]BZ, breathing zone.

personal samples. The remaining 176 (47%) were personal samples of the breathing zone (BZ) of operators (140 samples) or technicians (36 samples). In the semiconductor industry, the term "operator" applies to persons operating production equipment involved "on the line" in the fabrication area (manufacturing). The term "technician" applies to persons whose primary job function is either the maintenance, adjustment, or profiling of production equipment or delivery/removal of chemicals used in or on the equipment.

Exposure to 2-Ethoxyethanol (2-EE)

As shown in Table 8, a sufficient number (32) of time-weighted average (TWA) personal samples were collected for persons working with 2-EE. The average concentration in air was 0.55 ppm, which is about 1/400th the current OSHA PEL (200 ppm) and about 1/10th the ACGIH TLV established in 1984 (5 ppm). More importantly, the geometric mean (GM) for these data is 0.36 ppm—about 30% smaller than the mean. This indicates that, as expected, the typical concentration to which this group was exposed is less than that suggested by the arithmetic mean. The geometric standard deviation (GSD) was 3.65 for this data set, suggesting that there is a fairly broad range over which the data are distributed.

The short-term personal samples averaged 0.56 ppm and had a geometric mean of 0.16 ppm. The lesser geometric mean suggests that the

TABLE 8. Summary and Statistical Analysis of Industrial Hygiene Air Sampling Data for 2-Ethoxyethanol (2-EE)

Sampling data[a]	*N*	Range	Mean ± SD	Geometric mean ± GSD
Personal (TWA)	32	0.03–0.7	0.554 ± 0.280	0.357 ± 3.651
Personal (short-term)	4	0.3–2.0	0.563 ± 0.959	0.164 ± 5.917
Area (TWA)	24	0.05–1.1	0.992 ± 0.195	0.969 ± 1.263
Area (short-term)	20	0.06–2.0	1.03 ± 1.372	0.346 ± 11.935

[a]All concentrations are in ppm (v/v).

bulk of the samples were close to the limit of detection of the assay and that several high results skewed the mean. These results, however, are consistent with the TWA sampling results and are lower than might be expected, since short-term samples are generally collected in an effort to identify those jobs or tasks that are expected to pose the greatest exposure potential.

A total of 24 "area samples" was collected, and these had an arithmetic mean of 0.99 ppm with a geometric mean of 0.97 ppm and geometric standard deviation (GSD) of 1.26. Like the short-term personal samples, area samples are generally used to identify those tasks where the concentration of the air contaminant is likely to be highest. The good agreement between the mean and geometric means and the very small GSD suggests that, in the vast majority of situations, the maximum anticipated personal breathing zine concentrations (time-weighted average) of 2-EE in the semiconductor industry are well below 1.0 ppm. Although the number of short-term area samples is too small to be significant, the arithmetic mean and GM are consistent with other sampling data.

Even though GSDs in the range of 3–5 are larger than that frequently reported in the literature (Busch and Leidel, 1985), they are not unusual, and perhaps are typical of those observed in firms who have industrial hygiene programs. There are several reasons why relatively large GSDs can be expected in this study. First, whenever the arithmetic mean and geometric mean are close to the limit of detection of the assay, even samples as low as 1 ppm can markedly affect the GSD. Second, the studies that have been published by universities and NIOSH that suggest that GSDs in the range of 2.0 are more typical of a well controlled workplace were obtained in settings much different from those addressed in surveys within industry. For example, the university studies are generally obtained in a relatively small population of workers, involve 1 company, often involve 1 or 2 production areas (often within the same building), usually are collected over only 1 or 2 wk of time, and are usually collected during only 1 season of the year. In short, these studies often describe employee exposure over a relatively "narrow" window in time and for only one kind of process or job description.

In contrast to studies involving rather narrowly defined workplaces, this data set was gathered from seven different firms. Samples were obtained from numerous semiconductor manufacturing processes, from buildings containing various kinds of local exhaust and general ventilation, and with differing sampling times as well as other differences. Consequently, the GSD observed in this study, although greater than desired, is not surprising.

Exposure to 2-Ethoxyethanol Acetate (2-EEA)

Table 9 summarizes the results of 357 samples of 2-EEA. Personal samples were collected on 98 different occasions for periods of about 6–8 h,

TABLE 9. Summary and Statistical Analysis of Industrial Hygiene Air Sampling Data for 2-Ethoxyethanol Acetate (2-EEA)

Sampling data[a]	N	Range	Mean ± SD	Geometric mean ± GSD
Personal (TWA)	98	0.001–0.5	0.05 ± 0.08	0.02 ± 4.82
Personal (short-term)	21	0.001–18.0	2.82 ± 5.41	0.09 ± 32.77
Area (TWA)	128	0.001–1.8	0.05 ± 0.16	0.01 ± 6.08
Area (short-term)	10	0.005–15.0	1.56 ± 4.72	0.06 ± 10.66

[a]All concentrations are in ppm.

with certain samples collected over periods of 12 h. The arithmetic mean for these samples was 0.05 ppm, the GM was 0.02 ppm, and the GSD was 4.8. The data range in value from the limit of detection of 0.001 ppm to a maximum of 0.5 ppm. These results indicated that persons in the wafer manufacturing process are generally exposed to levels less than 0.05 ppm.

The results of short-term personal sampling which were collected for periods of about 15 min, indicate that the average level of exposure was about 2.8 ppm and that the geometric mean was about 0.10 ppm with a GSD of 33. Based on these data and the enormous GSD, one can not describe the likely range of short-term exposures. However, in light of the ample number of personal samples and a peak of concentration of 18 ppm, it is unlikely that short-term samples would rarely exceed 20 ppm.

The 128 area samples, which represent a much more sturdy data set than the short-term personal samples, indicate that exposures in those manufacturing areas that were thought to have the highest concentration of 2-EEA are very low. Specifically, the arithmetic mean was 0.05 ppm and the GM was 0.01 with a GSD of 6. The short-term area samples indicate that when samples were collected during the tasks believed to produce the highest levels, the airborne concentrations were in range of 1.0–2.0 ppm.

Exposure to 2-Methoxyethanol (2-ME)

As shown in Table 10, fewer personal and area samples were collected for 2-ME rather the other glycol ethers. Six personal TWA samples were collected, and they ranged in value from the limit of detection of 0.03 ppm to 0.80 ppm. The arithmetic mean of these samples was 0.22 ppm and the GM was 0.095 ppm with a GSD of 3.3. These data suggest that the bulk of the TWA samples were in the vicinity of 0.10 ppm.

Only one short-term personal sample was collected and one short-term area sample was collected. The data are virtually uniformative. Only

TABLE 10. Summary and Statistical Analysis of Industrial Hygiene Air Sampling Data for 2-Methoxyethanol (2-ME)

Sampling data[a]	*N*	Range	Mean ± SD	Geometric mean ± GSD
Personal (TWA)	6	0.04–1.0	0.22 ± 0.38	0.09 ± 3.30
Personal (short-term)	1	NA[b]	26.0 ± 0.0	NA
Area (TWA)	4	0.03–0.8	0.23 ± 0.38	0.08 ± 4.72
Area (short-term)	1	NA[b]	26.0 ± 0.0	NA

[a]All concentrations are in ppm (v/v).
[b]NA means not applicable.

4 area samples were collected, and these showed an average concentration of 0.23 ppm with a geometric mean of 0.08 ppm and a GSD of 4.7. This relatively high GSD is not uncommon in light of the small number of samples collected.

Exposure to 2-Methoxyethanol Acetate (2-MEA)

2-MEA was studied more thoroughly than 2-ME, and the results are summarized in Table 11. Sixteen personal samples were collected, and these indicate that the average airborne concentration of 2-MEA was 0.01 ppm and that the geometric mean was 0.01 ppm with a GSD of 1.0. As suggested by the GSD, none of the samples contained levels in excess of the limit of detection of the analytical method (0.01 ppm). Only one short-term personal sample was collected and only one short-term area sample was collected; consequently, no conclusions can be reached about these exposures.

None of the 20 area samples, which represent a substantial data set, showed vapor concentrations in excess of the limit of detection (0.01 ppm). As a result of the GSD of 1.0 (which indicates that there was no variability in the data set), one can, with reasonable confidence, infer that concentrations of 2-MEA will usually be lower than 0.01 ppm.

RISK ASSESSMENT

In the EPA's guidelines for assessing the risks posed by developmental toxicants, the EPA (1986) stated that:

> At present, there are no mathematical models that are generally accepted for estimating developmental toxicity responses below the applied dose range. This is due primarily to the lack of understanding of the biological mechanisms underlying developmental toxicity, intra/interspecies differences in the type of developmental events, the influence of maternal effects on the dose-response curve, and whether or not a threshold exists below which no effect will be produced by an agent. Many developmental toxicologists assume a threshold for most developmental effects; this as-

TABLE 11. Summary and Statistical Analysis of Industrial Hygiene Sampling Data for 2-Methoxyethanol Acetate (2-MEA)

Sampling data[a]	*N*	Range	Mean ± SD	Geometric mean ± SD
Personal (TWA)	16	0.01	0.01 ± 0.00	0.010 ± 1.00
Personal (short-term)	1	NA[b]	17.0 ± 0.0	NA
Area (TWA)	20	0.01	0.01 ± 0.00	0.010 ± 1.00
Area (short-term)	1	NA	18.0 ± 0.0	NA

[a]All concentrations are in ppm (v/v).
[b]NA means not applicable.

sumption is based largely on the biological rationale that the embryo is known to have some capacity for repair of the damage or insult and that most developmental deviations are probably multifactorial in nature. The existence of a no-effect level (NOEL) in an animal study does not prove or disprove the existence or level of a true threshold; it only defines the highest level of exposure under the conditions of the test that are not associated with a significant increase in effect. The use of NOELs and uncertainty factors or margins of safety are attempts to ensure that the allowable levels are below those that will produce a signigicant increase in developmental effects.

The *uncertainty-factor* approach to setting limits of exposure is conceptually a simple one. The no-observed-effect level (NOEL) is identified from studies (generally involving laboratory animals, but occasionally involving humans) that have been appropriately designed and conducted to assess the toxicological endpoint of interest. *Uncertainty-factors* are arithmetic factors of varying magnitude (10, 50, 100, or 1000) that are applied to the NOEL to account for biological variances so that experimentally derived data can be extrapolated for setting limits of human exposure. In general, safety factors have been identified for most forms of chemical toxicity except, perhaps, cancer and heritable mutations. For example, it has been customary to add a 2000-fold safety factor to the 90-d NOEL for neurotoxic agents when establishing a tolerance (based on acceptable daily intake) for pesticides that might be present in foods. A 100-fold safety factor has often been applied to the NOEL obtained in a chronic toxicity study to estimate the acceptable daily intake of food additives. Numerous developmental biologists, toxicologists, and physicians have indicated that the safety-factor approach should also be appropriate for establishing safe levels of exposure to developmental toxins.

For many years, the "margin of safety" approach has been used by regulatory agencies both here and abroad to assess the risks associated with particular exposure scenarios (Lehman and Fitzhugh, 1954; Weil, 1970, 1972; Calabrese, 1978; National Research Council, 1980; Hogan and

Hoel, 1982; Dourson and Stara, 1983; Gaylor, 1983; Johnson, 1984). Basically, a *margin of safety* is the ratio of the no-observed-effect level noted in animals (in this case, effects on offspring) and the dose to which persons are expected to be routinely exposed. The greater the difference between the animal NOEL and the anticipated human uptake, the greater is the margin of safety, and therefore, the greater the degree of protection. Margins of safety can also be defined as the difference between an acceptable level of exposure, such as an acceptable daily intake (ADI) or an occupational exposure limit (e.g., TLV) and the level of human exposure. One advantage is that it provides a quantitative framework by which scientists, regulators, and the public can easily assess the degree of risk, or conversely, the freedom from harm, when a chemical is used in a particular way.

Overview of Risk Calculations

The calculations shown in Table 12 are the basic ones used in this assessment. For this analysis, the margin of safety (MOS) was defined as the ratio of the TLV (e.g., safe level of exposure) and the geometric mean workplace air concentration. This appears to be the best available method for estimating the risk associated with developmental toxicants. For those chemicals where the TLV was not established to prevent adverse effects on development, the NOEL for developmental effects in a segment II study divided by a factor of 100 could be used as a "preliminary exposure limit" (since this would represent the estimated human dose considered safe) if the A/D ratio was 5 or less. When assessing the risk of developmental toxins, professional judgment needs to be exercised in selecting the appropriate uncertainty factor since it should be influenced by the A/D ratio, the severity of the adverse effect, the similarity of results between species, the metabolic differences between spe-

TABLE 12. The *A/D* Ratios for Selected Glycol Ethers and the Associated Risks for Workers Studied in the Semiconductor Industry (Based on Margins of Safety)

Chemical	Hazard (*A/D* ratio)	Margin of safety (TLV/exposure)[a]
2-Ethoxyethanol (ethylene glycol monoethyl ether or cellosolve)	1-5	14
2-Methoxyethanol (ethylene glycol monomethyl ether or methyl cellosolve)	3-5	53
2-Ethoxyethanol acetate (ethylene glycol monoethyl ether acetate)	3-5	250
2-Methoxyethanol acetate) (ethylene glycol monomethyl ether acetate)	4	500

[a]Margin of safety is defined as the current TLV divided by the geometric mean exposure of employees.

cies, and human experience. The margins of safety calculated in this analysis were probably greater than the actual value, since the limit of detection for the air samples, rather than zero, was used in calculating the geometric mean exposure level.

Tests for developmental toxicity indicated that maternal exposure to 2-ME produced no adverse effects of pregnant adult rats and mice exposed to 10 ppm. Adverse effects on offspring were observed in mice exposed to about 50 ppm. In a 13-wk experiment wherein rats and rabbits were exposed, a NOEL of 30 ppm was clearly identified. Based on all the available data, a NOEL of 10 ppm (in animals) seems to be a reasonable one on which to develop a quantitative evaluation of 2-ME.

Based on typical exposures in the semiconductor industry and the most appropriate occupational exposure limit, the TLV, the estimated MOS is 53. This MOS suggests that the risk of adverse effects on the offspring of exposed parents is insignificant for those employees who minimize or prevent dermal contact. Assuming that the TLV has been set at a level that was intended to protect the fetus, a margin of safety of 1 indicates that persons and their offspring can, in general, be exposed to this hazard, yet not be at significant risk of injury.

Tests conducted by Andrews et al. (1981) and Tinston et al. (1983d) indicate that adult pregnant rats exposed to 200 ppm of 2-EE were not adversely affected and no effects on development were observed in the offspring of mothers exposed to 50 ppm. It is noteworthy that there is a 10-fold difference between the 1986 TLV (5 ppm) and the inhalation dose that caused no adverse effects in animals. The 53-fold margin of safety between the TLV and the typical workplace air concentration suggests that this chemical is well controlled and that the offspring of pregnant workers should not be at an increased risk of adverse effects, assuming that dermal exposure is minimal.

The teratogenic potency of 2-EEA is roughly the same as the parent chemical, 2-EE (Table 12). There is a fourfold difference between the dose that produced adverse effects on pregnant rabbits (100 ppm) and the dose at which no adverse effects were noted in offspring (25 ppm). The results of workplace air monitoring indicate that in the semiconductor industry, the airborne concentrations are quite low (0.02 ppm), thus providing a margin of safety sufficiently large that the offspring of pregnant workers should not be at increased risk as long as dermal exposure is minimized.

Pregnant adult animals and their offspring do not show adverse effects when exposed to 25 ppm. As shown in Table 12, the developmental toxicity of 2-MEA is approximately that of 2-EEA. The data indicate there is a significant difference between the dose (vapor concentration × time) that produced adverse effects in the mother compared to the fetus (fourfold). Assuming that these data represent typical workplace exposures, the airborne concentrations are almost 5000-fold lower than the

NOEL for offspring observed in animal studies. Consequently, assuming that skin contact is prevented, or minimized, the offspring of pregnant workers in this industry should be at virtually no adverse risk of developmental toxicity.

SKIN ABSORPTION

During much of the past 40 years, the quantitative uptake of solvents through the skin of workers has been poorly understood and, consequently, often neglected by occupational health professionals. Recently, however, a number of toxicologists have developed tests to estimate the rate of dermal uptake using test animals and/or the skin of human cadavers. Jepson et al. (1985) and McDougal et al. (1986) have developed some of the most sophisticated and accurate tests for estimating dermal uptake of vapors and liquids by animals. Dugard et al. (1984) and Guest et al. (1984) have specifically evaluated the dermal uptake of the glycol ethers. One shortcoming of animal tests is that human skin has generally been shown for a diverse class of chemicals to be less permeable to xenobiotics than the skin of rabbits and rats (Bartek and LaBudde, 1975; Wester and Noonan, 1980).

Dugard and co-workers (1984) studied human skin (in vitro) and found that of the eight glycol ethers studied, 2-methoxyethanol (2-ME) was most readily absorbed (mean steady rate 2.82 $mg/cm^2 \cdot h$). For the monoethylene glycol ethers, they observed a reduction in the rate of absorption with increasing molecular weight or decreasing volatility (2-EE, 2.82 $mg/cm^2 \cdot h$; 2-ethoxyethanol, EE, 0.796 $mg/cm^2 \cdot h$; 2-butoxyethanol, 2-BE, 0.198 $mg/cm^2 \cdot h$) and also observed it within the diethylene glycol series: 2-(2-methoxyethoxy) ethanol (DM, 0.206 $mg/cm^2 \cdot h$); 2-(2-ethoxyethoxy) ethanol (DE, 0.125 $mg/cm^2 \cdot h$), and 2-(2-butoxyethoxy) ethanol (DB, 0.035 $mg/cm^2 \cdot h$). The rate of absorption of 2-ethoxyethyl acetate (2-EEA) was similar to that of the parent glycol ether, 2-EE. The absorption rates of diethylene glycol ethers were slower than their corresponding monoethylene glycol equivalents.

These authors noted that the results of their studies employing undiluted glycol ethers should not be extrapolated directly to solvent mixtures on a "rate proportional to concentration" basis, because components of the mixture may have a variety of effects on the absorption process. Based on their work, however, approximate absorption rates can be calculated for the most common glycol ethers.

Guest and co-workers (1984) studied the rate of absorption of 2-EEA and 2-propoxyethyl acetate (2-PEA) in the beagle dog. Male beagle dogs were exposed to 50 ppm PEA or EEA for 5 h, and breath samples were collected during the exposure and a 3-h recovery period. Both compounds were rapidly absorbed through the lungs. After 10 min of exposure, the concentrations of the parent compounds in the expired breath

were 5–10 ppm (80–90% absorption) and reached plateau values at about 3 h of 13 ppm for PEA (74% absorption) and 16 ppm for EEA (68% absorption). For studies of percutaneous absorption, [^{14}C]PEA or [^{14}C]EEA was added to undiluted compound and applied in a glass cell to a shaved area on a dog's thorax for 30 or 60 min. Blood and expired air were collected for 8 h and urine for 24 h. The pattern of urinary elimination for each compound was similar to that seen after iv dosing, with [^{14}C]PEA being excreted more rapidly than [^{14}C]EEA. Although the excretion rates for the two compounds were markedly different, the absorption rates were similar. Estimated over a 60-min period, the percutaneous absorption rate was 110 nmol/cm^2·min for EEA. This values is similar to those for other lipid-soluble compounds.

Although only about 30–60 chemicals have been studied in human skin (in vivo and in vitro), it appears that these four glycol ethers penetrate the skin at a rate similar to other solvents. For example, Piotrowski (1973) determined that the dermal uptake of benzene, aniline, and toluene in humans (in vivo) was 0.4 mg/cm^2·h, 0.5 mg/cm^2·h, and 0.5 mg/cm^2·h, respectively. Dugard et al. (1984) noted that compared with other solvents that have been measured using human epidermis, 2-ME has a very high dermal absorption rate. Specifically, 2-ME penetrated the skin over 3 times more efficiently than 2-EE and 2-EEA, and about 10 times more efficiently than 2-butoxyethanol. Further, 2-ME penetrates skin 4 times more efficiently than ethanol and 40 times more efficiently than n-butanol. Dugard et al. have noted that the rapid absorption through human skin is in agreement with the clinical observations and results of pharmacokinetic studies by others who have studied 2-ME.

To illustrate the potential importance of skin absorption as a route of entry for the glycol ethers, consider the following example:

Scenario 1: Most of the glycol ethers have skin designations accompanying their TLVs, as do common solvents such as benzene, aniline and trichloroethylene. Experimental data in animals (in vivo) and in humans (in vitro) indicate that the glycol ethers pass through the skin much like these solvents. For the sake of illustration, one can estimate how much 2-ME could possibly be absorbed (on an mg/kg basis), if a person has a heavily contaminated glove on one hand for about 30 minutes?

1. Surface area of the hands: 400 cm^2 (Snyder, 1975)
2. Exposure time: 30 min
3. Rate of absorption: 2.8 mg/cm^2·h

Uptake:

$$(400\ \text{cm}^2)\ (2.8\ \text{mg/cm}^2\cdot\text{h})\ (0.5\ \text{h})\ (\text{person}/70\ \text{kg}) = 8\ \text{mg/kg}\cdot\text{d}$$

Scenario 2: By comparison, how much 2-ME will be taken up by a 70-kg employee who is exposed for 8 h/d at the TLV of 5 ppm (16 mg/m^3) assuming an 80% uptake efficiency?

Uptake:

$$(16\ mg/m^3)\ (10\ m^3/8\ h\ workday)\ (0.8\ uptake)\ (person/70\ kg) = Y$$
$$Y = 1.8\ mg/kg \cdot d$$

In this example, it is assumed that a glove is heavily contaminated with 2-ME. The calculations indicate that dermal uptake could be as much as 8 mg/kg·d following thirty minutes of exposure. This dose is about 4 times greater than the predicted uptake of 2-ME when a person works for 8 h in an environment containing 2-ME at the TLV concentration. From this example, it is clear that the dermal route of entry can significantly contribute to the total absorbed dose.

Based on the above data, a worker who is reasonably careless with respect to his personal hygiene could easily take up as much or more of the glycol ethers through skin contact than that taken up by inhalation of vapors at the TLV. Since the airborne concentrations of these glycol ethers in the semiconductor industry are a fraction of the current TLV, dermal uptake could easily be more important than inhalation.

DISCUSSION

The available toxicology data on these glycol ethers indicates that they can produce phase specific developmental effects on offspring of pregnant animals. As noted by Johnson (1987), the *A/D* ratio for these chemicals is typically in the range of 1–5. Although the *A/D* concept is a relatively new one and additional data would be useful to further confirm its merits, these values for *A/D* are sufficiently high to suggest that their potential hazard to human should not be underestimated. Situations where dermal exposures are not well controlled could pose not only a significant hazard to adults, but also to the fetus. Biological monitoring would be most useful to estimate uptake of these kinds of chemicals which can be readily absorbed through the skin and it appears that methods are currently available for these four glycol ethers (NIOSH, 1986; Smallwood et al., 1987).

The results of the developmental toxicity tests, coupled with the workplace exposure data, indicate that workers in the semiconductor industry are exposed to levels of these glycol ethers that should not place them or their offspring at risk of adverse effects. The human hazard posed by these chemicals (*A/D* of approximately 5) is moderate. For comparison, the A/D ratio for thalidomide was about 20 for the four species tested. Among the four chemicals studied, the margin of safety for 2-EE is the smallest (14), while 2-MEA has the largest (500).

It has been suggested that humans may have a more complex biological system for recognizing other-than-normal developing embryos, and this may account for the high spontaneous abortion rate in humans. Others have postulated that the human embryo has a more sophisticated

detoxification and repair mechanism than lesser species, thus lessening the risks of adverse effects of exposure to xenobiotics. Unfortunately, such speculation simply suggests that we have more to learn about developmental toxicants. Physiological pharmacokinetic differences—i.e., those differences between species such as average heart rate, surface area to weight ratios, ventilation rate, biochemical constants (e.g., V_{max} and K_m), and percent body fat—suggest that where the metabolite is the toxic moiety, for a given dose, animals are likely to be at greater risk of adverse developmental effects. Although no published papers have specifically addressed this phenomenon with respect to developmental toxins, some insight may be obtained from recent publications that discuss techniques for estimating the toxic and carcinogenic response in humans based on the scale-up of animal data (Ramsey and Andersen, 1984; Andersen et al., 1987).

There are a number of uncertainties inherent in any risk assessment of a developmental or a reproductive toxicant. Although our current understanding of reproductive biology and toxicology suggests that the approach that has been used here should accurately describe the human health hazard, some assumptions and uncertainties should be recognized. First, metabolic differences between animals and humans are not uncommon, and these are difficult to predict (Calabrese, 1983). Such differences can result in greater or lesser production of toxic or nontoxic metabolites by humans when compared with lower species (rat or rabbit). In the case of the glycol ethers, such differences appear small given the similarity of the metabolic products between the four species exposed to 2-butoxyethanol (Carpenter, 1956). Miller et al. (1983a, 1984; Jonsson and Steen, 1978) have suggested that the 2-ME is likely to be metabolized by humans and rodents in a similar fashion. Perhaps the greatest uncertainty and concern is the possibility that the test species will underestimate the human hazard due to a simple difference in susceptibility.

The possibility of delayed developmental effects in offspring also introduces some uncertainty into the risk assessment process. The field of behavioral teratology, which has been of considerable interest in recent years, has not yet developed "rules of thumb" that give much insight whether the offspring of humans are likely to be more or less susceptible to a given agent than the offspring of rodents. The purpose of segment II test is not to identify those chemicals that might produce subtle adverse effects on the intellectual capabilities of offspring, and tests that might be helpful in assessing this hazard have yet to be fully developed.

Even though there are a number of uncertainties in assessing the human developmental hazard using animal studies, the historical experience of the 1970s and 1980s suggests that segment II studies are an accurate and sensitive identifier of chemicals that might produce adverse effects on offspring. Since in these tests pregnant mothers are exposed

to fairly significant levels of the test substance on every day following conception, through predifferentiation, early differentiation, proliferation, early growth, and organogenesis, we can feel confident that the tests aggressively challenge both the mother and the offspring during the most critical periods in the pregnancy.

Based on our understanding of the biological mechanisms surrounding developmental effects, and the susceptibility of rodents and rabbits, numerous scientific bodies and regulatory agencies have concluded that a threshold dose exists below which no adverse effects on offspring should exist. The exact nature of the developmental effects produced by a chemical may not always be identified in humans and experimental animals, but the concentrations (doses) at which developmental effects are produced tend to be very similar, and only rather modest safety factors (Nesbit and Karch, 1983; Hemminki and Vineis, 1985) are needed to allow the tests on these animals surrogates to provide a high level of protection for the human embryo. Specifically, if human exposures are maintained at levels about 1/100th the NOEL observed in animal studies, experience suggests that the offspring of exposed persons should not be at risk of adverse effects. Uncertainty factors as low as 10 may be appropriate in situations where ample experimental data or favorable human experience is available. Historically, the size of the uncertainty factor used to set acceptable levels of exposure for environmental contaminants has been different than that used in the occupational setting, justified primarily by the lesser number of exposured persons and the concept of voluntary risk. The size of the uncertainty factor can arguably be the responsibility of either the risk assessor or the risk manager.

The available data on the reproductive and developmental toxicology of these glycol ethers should be sufficient to give a good indication of their qualitative and quantitative potential to adversely affect the offspring of exposed workers. By applying the concepts that have been discussed, and by using the inhalation exposure data that has been collected within the semiconductor industry, it can be concluded that workers and their offspring should not be at increased risk of adverse effects due to exposure to these glycol ethers, as long as airborne concentrations are maintained at current levels and dermal contact is avoided.

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