MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

September 25, 1996

TO: File for Diethyl Ether (CAS # 60-29-7)

FROM: Dan O'Brien, Toxic Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level (ITSL) for Diethyl Ether

The initial threshold screening level for diethyl ether is 12,000 $\mu g/m^3$ based on a 8 hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: AQD chemical files, IRIS, HEAST, ACGIH TLV Booklet, NIOSH Pocket Guide to Chemical Hazards, RTECS, NTP Management Status Report, EPB Library, IARC Monographs, CAS On-line and NLM/Toxline (1967 January 23, 1996), CESARS, Patty's Industrial Hygiene and Toxicology, Merck Index and Condensed Chemical Dictionary.

Diethyl ether (DE) is a colorless, hygroscopic, volatile liquid with an aromatic odor and a sweet, burning taste (Merck, 1983; Hawley, 1981). Mobile and highly flammable, it is widely used as a solvent for waxes, fats, oils, perfumes, alkaloids, gums and nitrocellulose. It has important applications in organic synthesis, and is used as an easily removable extractant of active principles from plant and animal tissues. Other applications include uses in analytical chemistry, in the manufacture of gun powder and as an inhalation anesthetic (Verschueren, 1983).

With respect to acute toxicity, RTECS (1996) reports a rat oral LD_{50} of 1215 mg/kg for DE, in addition to lethal inhalation concentrations for several species, including rats (LC_{50}=73000 ppm [221 g/m^3] for a 2 hour exposure), mice (LC_{50}=6500 ppm [19.7 g/m^3] for a 99 minute exposure), dogs (LC_{Lo}=76000 ppm [230 g/m^3]) and rabbits (LC_{Lo}=106000 ppm [321 g/m^3]). One acute study was executed to investigate a possible age-related susceptibility to the lethal effects of DE (Schwetz and Becker, 1971). Pregnant adult Sprague-Dawley rats were allowed natural parturition and the litters were maintained with their dams for 24-48 hours. A 10 L exposure chamber was fitted with a pump and vaporizer as a closed circuit anesthetic apparatus. Ten adult rats (275-325 g) and forty neonatal rats (5-8 g) were exposed to initial DE concentrations of 15 to 20 volume %[1]; one adult rat and four rat pups of either sex were exposed in the chamber at a single time. The animals were observed at 0.14 log time intervals, and at those same intervals, ether concentrations in the exposure chamber and in the blood of similarly exposed animals were determined by gas chromatography (GC). Blood ether concentrations at median time to death (LT_{50}) were determined from blood ether-time plots for the adults and for the pups. For those rats exposed to 15 volume %, LT_{50} values (95% confidence limits) were 21 minutes (18-24) for the adults and 135 minutes (123-148) for the neonates, while among those exposed to 20 volume %, the adult LT_{50} was 17 minutes (14-20) and the neonatal LT_{50} was 86 minutes (80-92). Calculated blood DE concentrations corresponding to those LT_{50}s were 46, 142, 65 and 159 mg/100 ml, respectively. While the lethality curves for neonates and for adults were parallel (suggesting that the mechanism of death may be the same in each age group)

[1] Since the system was closed and ether was not replenished as it was absorbed by the rats, the actual DE concentrations at LT50 were likely somewhat less than the initial concentrations.

the neonatal rats were clearly more resistant to lethal concentrations of DE than were the adults. The authors forwarded two hypotheses for the resistance of the neonates: 1) decreased susceptibility of the neonatal brain to medullary depression and 2) decreased absorption of DE by young rats. Since the blood concentrations in the neonates were found to be 2.5-3 times those in the adults at LT_{50}, their blood concentrations reflected their longer exposure, and decreased absorption cannot explain their relative resistance to DE lethality. Consequently, it was concluded that the resistance was due to some sort of decreased sensitivity of the neonatal nervous system. While not valuable for setting a screening level, this study nonetheless seems worthy of attention, in that it suggests that young animals are less sensitive to lethal effects of DE exposure, and to the extent that the pharmacokinetics of DE are similar between humans and rats, raises the possibility that some effects in young humans might be less severe at a given level of DE exposure than those in human adults.

A unique approach was taken by Glowa (1993) attempting to assess the neuroendocrine and behavioral effects of DE exposure, characterize their dose-response relationships, and antagonize those effects using physical stresses. Male NIH-white mice were exposed to DE in inhalation chambers for five to thirty minutes to concentrations ranging from 1000 to 30,000 ppm (3030-90,900 mg/m^3). Behavioral responses were assessed using a fixed interval schedule of milk presentation. The study recorded "large increases in both behavioral and neuroendocrine responses in the mouse at concentrations much less than those required for anesthesia", but the dose-response relationship was not linear. Thirty minute exposure to 1000 ppm caused minimal effects. While 3000 to 10,000 ppm exposures doubled the rates of increased response, concentrations higher than that decreased responses almost completely. Five minute exposures over the same range of concentrations produced concentration-related effects which were of a lesser magnitude than those produced by the 30 minute exposures. Again, while not especially helpful for setting a screening level, the study is still worthy of note because it emphasizes that the dose-response relationship for DE is non-linear.

Searches noted a subacute repeat inhalation study of DE conducted in rabbits, rats and guinea pigs simultaneously (Chenoweth *et al.*, 1972). Groups of 20 Wistar rats (10/sex), 12 guinea pigs (6/sex) and 4 rabbits (2/sex) were exposed in inhalation chambers to subanesthetic concentrations of 2000 ppm (6060 mg/m^3) DE or to filtered room air for 7 hours per day, 5 days per week for a total of 7 weeks. The exposure concentration was chosen by averaging the equipotent anesthetic doses of DE reported for dogs and humans, and reducing each value by a factor of ten. Nominal concentrations of DE in the exposure chamber were calculated, and chamber concentrations of DE were "analyzed periodically throughout the exposures" by infrared spectrophotometry. Health endpoints monitored included clinical signs (alterations in activity, symptoms of eye and nasal irritation, skin condition, and respiratory distress), body weights (three times weekly), limited hematology and serum biochemistry (cell counts, packed cell volume [PCV], hemoglobin [Hb] concentration, alanine transaminase [ALT], aspartate transaminase [AST]), organ to body weight ratios (for lung, liver, kidney, heart, spleen and testes), and gross and histopathology. ALT and AST were determined only for "representative groups", while the other endpoints were determined for all animals. Statistical analysis consisted of testing differences in means *via* Student's *t* test; a p-value of 0.01 was considered statistically significant. Mean DE concentration in the exposure chamber over the course of the experiment was 1908±208 ppm (5781 mg/m^3). None of the endpoints evaluated exhibited significant differences between the DE-exposed group and controls in any of the three species under study. While not stated explicitly by the authors, the single exposure level tested could be considered a no-observed effect level (NOEL).

A substantial body of literature exists describing the absorption, distribution and metabolism of DE; this is summarized nicely by Elvestad *et al.* (1993). Absorption of DE through the lungs occurs quickly at the onset of inhalation exposure, and excretion by post-exposure exhalation, the primary route of elimination, is also rapid (Kirwin and Galvin, 1993). Dermal absorption over intact skin is reported to be of no consequence in humans, although repeated and prolonged applications to the skin can result in slight irritation. The compound is also irritating to mucous membranes and the eye. In the body, DE has an affinity for lipids, and rapidly accumulates in fat and in the brain, where it persists at relatively high concentrations for some time after ambient and blood concentrations have decreased. It has been estimated that about 8-10% of absorbed DE is metabolized in the body, with the remainder excreted unchanged through the lungs (NEG/NIOSH, 1993) Urine serves as a minor route of excretion, although the concentration in urine does not exceed that in the blood perfusing the kidneys. According to Van Dyke and Chenoweth (1965), the proposed metabolites of DE are carbon dioxide, ethanol and acetaldehyde; later references (NEG/NIOSH, 1993) confirm two of these (ethanol and acetaldehyde) are produced by oxidation of DE by inducible hepatic microsomes. The metabolites are, in turn, oxidized to acetate, which then enters the two carbon pool of intermediary metabolism. With respect to pharmacokinetic data, Poulin and Krishnan (1995) and Gargas *et al.* (1986) have investigated tissue:blood partition coefficients for DE. In addition, some research effort (Shelley *et al.*, 1989) has been directed toward the development of computer-implemented physiologically based pharmacokinetic (PBPK) models for nursing infants exposed to volatile organic compounds (VOCs) *via* their mothers. Watanabe and Kuwabara (1994) have suggested an interaction between ether metabolism and ammonia metabolism in the liver, based on their findings of elevated blood ammonia concentrations in rats following inhalation anesthesia with DE. Ammonia concentrations were highest in animals whose liver function had been previously compromised by carbon tetrachloride exposure and in those exposed to indomethacin; phenobarbital exposure did not effect blood ammonia levels. The effects of DE inhalation on glycemia and some variables of intermediate metabolism have been studied in rats by Perez-Llamas and co-workers (1992). DE was found to significantly increase plasma glucose in starved Wistar rats, while concentrations of triglycerides, cholesterol and phospholipids were not significantly altered. Urine ketones, and blood CO_2 levels were increased, while blood pH was lowered. The authors speculated that the increases in glucose were multifactorial in origin, due not only to stress, but to increased releases of catecholamines and glucocorticoids, and to a decrease in glucose utilization at the tissue level. DE at concentrations of 25% was found not to effect the surface tension properties of surfactant obtained from the lungs of adult New Zealand rabbits (Enhorning *et al.*, 1986). Finally, as part of a larger study to illuminate mechanisms of blood transport for VOCs, Lam *et al.* (1990) studied the partitioning of DE in the plasma, erythrocytes, and plasma proteins of rats *in vivo* and *in vitro* and of humans *in vitro*. Groups of 4 or 5 male Sprague-Dawley rats weighing ~300 g were exposed to a steady-state DE concentration of approximately 500 ppm (1513 mg/m^3) for 2 hrs in an inhalation chamber, after which they were removed and decapitated immediately. Blood was then obtained for determination of DE distribution. In addition, rat plasma and blood and human plasma and blood were obtained and mixed with known concentrations of DE. In all cases, blood components were separated (erythrocytes, plasma, serum) and concentrations of DE in each component determined by GC. Further, for humans, concentrations were divided into subcomponents; hemoglobin (Hb), erythrocyte membrane, and red cell water for the red cell component, and plasma protein and plasma water for the plasma component. In rats, there was little difference between DE distributions obtained with *in vivo* methods versus *in vitro* methods; in both cases, about 48% of DE was partitioned to red cells, with the remainder in plasma. Interestingly, and

in contrast to more lipophilic solvents tested in the same study, the proportion of DE partitioned to erythrocytes was nearly the same (~46% vs. 48%) in humans as it was in rats, suggesting that at least with respect to distribution in blood, results in rats appear representative of results that might be obtained from humans. Subcomponent analysis in human blood and plasma showed ~28% of the plasma component of DE partitioned into plasma water, with the remainder in plasma protein, while in red cells, 32% of DE was recovered from red cell water, less than 1% from membrane, and ~52% was found associated with Hb. The authors acknowledge, however, that due to the methods employed, the actual proportions of DE partitioned to membranes and Hb were likely higher than those reported.

A concise summary of the toxicology of DE relevant to an occupational setting has been published by the Nordic Expert Group (NEG) and the U.S. National Institute for Occupational Safety and Health (NIOSH) (NEG/NIOSH, 1993)[2]. A somewhat shorter but well-executed review is that of Elvestad *et al.* (1993). The primary physiologic effect of DE in humans is narcosis and general anesthesia, which is induced and maintained at concentrations in the range of 19,000-150,000 ppm (57,600-455,000 mg/m^3) (ACGIH, 1991). In general, the human inhalation toxicity of DE in an industrial setting has long been considered low (NEG/NIOSH, 1993; Cook, 1945; Henderson and Haggard, 1943). Much of what is known about adverse human health effects caused by DE has been derived from reports of clinical signs in individuals who were deliberately intoxicating themselves. Clinical toxicology reviews concerning abuse of volatile substances such as DE include Dinwiddie (1994), Flanagan and Ives (1994) and Kunisaki and Augenstein (1994). A contemporary review of DE's use as a general anesthetic has been published by Farman (1981), and a relatively extensive review on this topic is also covered by NEG/NIOSH (1993). Clinical signs of DE exposure are reported to be dose-related (Flanagan and Ives, 1994), with small doses leading rapidly to euphoria and "other disturbances of behavior similar to those caused by ethanol", and may induce delusions and hallucinations. Higher doses may produce life-threatening effects, which may be either direct (coma, seizures, cardiac toxicity) or indirect (aspiration of vomitus). An older review (Amor, 1950) groups DE as a primary anesthetic, and characterizes the progression of anesthesia/toxicity into five stages:

1. Preliminary stage: Slight disturbance of judgment; decrease in accuracy of the co-ordination of finer movements; slowness in performing skilled work; increase in errors.
2. Confusion and bewilderment: Inco-ordination of movement; a stage of drunkenness.
3. Excitement: Loss of inhibition control.
4. The stage of complete surgical anesthesia: Muscular relaxation complete; cough and corneal reflexes disappear.
5. Abolition of the activity of the respiratory center: Death generally due to this effect.

Acute effects of DE exposure recorded in industry include irritation of mucous membranes and "ether jag", while chronic effects are listed as gastrointestinal disturbances, skin eruptions, inappetance, exhaustion, headache, sleepiness, dizziness, excitation, psychic disturbances and polycythemia (NEG/NIOSH, 1993; ACGIH, 1991; Amor, 1950; Henderson and

[2] This reference summarizes toxicity of DE on many body systems in both animals and humans, as well as information concerning metabolism, carcinogenicity and mutagenicity, and reproductive toxicity. The scientific literature concerning DE is very extensive, and data from other references cited in this screening level derivation are intended only to *complement* this summary document. The reader is referred to the NEG/NIOSH document for a more comprehensive treatment of DE literature relevant to human occupational exposure.

Haggard, 1943). Amor lists 24,800 mg/m^3 as a concentration "which will give rise to severe toxic effects" in persons exposed for one hour, 6200 mg/m^3, as a concentration "which, if exposure ... continues for more than a short time, may lead to symptoms of illness", and 1550 mg/m^3, as the general atmospheric concentration above which "unsatisfactory conditions" exist. The author does not discuss the data upon which these critical concentrations are based. Henderson and Haggard (1943) state that the arterial blood concentration required to produce surgical anesthesia is between 1.5 and 3 g/L of blood. Blood concentrations of 0.018 g/L and 0.09 g/L are associated by these authors with no signs of intoxication and with "dizziness in some individuals", respectively. The same source estimates that a 70 kg man inhaling 165 ppm (500 mg/m^3) could absorb a maximum of 0.52 g, and that that individual's blood concentration would be 0.0074 g/L, a concentration less than half the concentration which the authors report to be free from adverse effects. Some tolerance is probably developed to ether on repeated exposures so that concentrations which, at first, induce very mild intoxication may eventually cease to do so.

Literature concerning the toxicity of DE in humans *via* ingestion is extremely limited. Despite the fact that the agent is irritating to mucous membranes (NEG/NIOSH, 1993), it has nonetheless been ingested not uncommonly since the late 1800's (Bartholomew, 1962). Reports of the highest oral dose of DE which can be tolerated vary widely. As little as 30 ml (21.4 g) has been reported to be lethal (Moeschlin, 1986; Baselt, 1980); yet, clinical descriptions of individuals with "ether habits" suggest that as much as a liter a day has been ingested without fatal consequences (Bartholomew, 1962)[3]. While data are sparse, case reports of people addicted or habituated to DE suggest that oral exposure leads to clinical signs and symptoms which are somewhat different than those elicited by inhalation. Descriptions found in our searches suggest an intoxication more closely resembling alcoholism than the general anesthesia which characterizes inhalation exposure (NEG/NIOSH, 1993; Bartholomew, 1962; Anonymous, 1915). It has also been noted that those who abuse DE by inhalation tend to have a "more specific addiction" than those ingesting it (Bredemann, 1950). Although these clinical descriptions are subjective by nature and hardly recent, they do suggest that there may be substantial differences between the toxicity of inhaled DE versus ingested DE. Thus, caution appears to be indicated in extrapolating from oral toxicity data to characterize human health risks from inhalation exposures.

With respect to reproductive and developmental outcomes, Taskinen and co-workers (Taskinen *et al.*, 1994) conducted a retrospective case-control study of pregnancy outcomes among laboratory workers with multiple chemical exposures in Finland between 1973 and 1986. Two endpoints were studied: spontaneous abortions and congenital malformations, for which the number of participants in the final study populations were 535 and 141, respectively. Occurrence of low birthweight was also studied in conjunction with both of these outcomes. Self-administered questionnaires were used by the study subjects to report the tasks performed at work, and two occupational hygienists (blinded to pregnancy outcome status of the women) were employed to determine each subjects likely chemical exposures. Spontaneous abortions and congenital malformations were reported by the subjects and confirmed by cross-reference with disease registries. In logistic models, while controlling for the potentially confounding effects of employment, smoking, alcohol consumption, parity, previous miscarriages, failed birth control and febrile illness

[3] Note that for a 70 kg adult, these figures suggest that while a dose as low as 31 mg/kg can be lethal, a dose as high as 10,200 mg/kg may not be. This points out that the oral toxicity of DE in humans is not well characterized.

during pregnancy, exposure to DE was not associated with either spontaneous abortion (Odds Ratio [OR] = 1.0 (95% Confidence Interval [C.I.] 0.6-1.7, low exposure; OR = 0.5 (95% C.I. 0.3-1.5), high exposure) nor congenital malformation or low birthweight (ORs not given). No quantitative exposure assessment was performed in this study that might have allowed application of these results in a quantitative risk assessment. A review of the evidence for reproductive hazards of anesthetic gases as a class (primarily of nitrous oxide and halothane) has been published by Infante and Tsongas (1981). DE is mentioned only briefly by those authors, who cite a single reference (Smith *et al.*, 1968) which found diethyl ether to be toxic to chicken embryos. A cross reference to the same study by NEG/NIOSH (1993) notes that exposures ranged from 277-924 g/m^3 over a duration of 5 to 6 hours, and that the elevation in the rate of abnormal surviving embryos was statistically significant on days 3 and 4. Embryo death rates were extremely high (up to 96.1%). NEG/NIOSH also note that "the type of anomalies produced by ethyl ether exposure was the same as that induced by any generally toxic agent given at the same stage of development". Thus, the data assessing the possible reproductive and developmental effects of DE exposure are quite limited, and clearly inadequate as a basis for the derivation of a screening level.

Concerning data relevant to the carcinogenicity, our searches found reference made to DE by the International Agency for Research on Cancer (IARC) (1976), but no information specific to the chemical is presented. Making reference to several epidemiological studies of persons occupationally exposed to inhalation anesthetics as a class, IARC notes that "available studies indicated that working in the operating-room environment is associated with an increased risk of cancer, teratogenic effects and, possibly, mutagenic effects, but it is not possible at the present time to determine which particular factors are responsible". While no experimental studies were located in which DE was tested as a primary carcinogen, the promoting effect of DE on lung tumors induced in hamsters by a mixture of benzo[a]pyrene and ferric oxide (BaP/FeO) has been studied by Henry and Port (1978). These investigators instilled 0.2 ml of a suspension of 2% BaP[4] and 2% FeO in Normal saline into the tracheas of anesthetized hamsters, 8-9 weeks old, 50 males and 50 females per group, once weekly for 10 weeks. The study utilized three anesthetics: 1) methohexital sodium (Brevital), intraperitoneally (i.p.) administered, 2) DE, administered by inhalation, and 3) methoxyflurane, also administered by inhalation. The concentrations of anesthetic to which the animals were exposed are not reported, only that levels were sufficient to maintain a "light anesthetic state", and that animals were "kept in the anesthesia apparatus for 5-10 minutes" per exposure. All animals were then checked twice daily and weighed at 4 week intervals, and allowed to die spontaneously or were euthanized when moribund. All animals were necropsied at the time of death, "except a few that were lost through cannibalism". An additional 48 hamsters (6 groups of 4 males and 4 females) were included in the study; three groups were given the anesthetic only for 10 weekly exposures, and the other 3 groups were anesthetized and instilled, but were killed, 2 animals per group, after 5 and 10 instillations and after 2 and 4 months following the end of exposure. Average body weights of the hamsters were lower in the DE and Brevital-anesthetized groups compared to the methoxyflurane group, and by the end of the ten week exposure period, the DE group had the lowest average body weights. During the weeks of instillation, mortality was greatest in the Brevital group, with ~45% deceased by the end of 10 weeks. The authors considered only those deaths which occurred in the tenth week to be due to neoplasia. During the same 10 week period, ~30% of the DE anesthetized group died, while only ~14% of the methoxyflurane anesthetized group expired. Histopathological exams of the control animals (those exposed only to the anesthetics) noted a progressive

[4] The particle size distribution of the suspension was 60% < 3 μm, 35% from 3 to 15 μm, and 5% > 15 μm.

inflammation of the lungs characterized by a mild to moderate interstitial pneumonia with areas of congestion, septal edema, alveolar hemorrhage and emphysema. While these changes were present in both the DE and methoxyflurane-anesthetized groups, they were more severe in the DE animals. The authors presumed that the changes were due to the irritating effects of the inhalation agents, as there were no lung lesions exhibited in the Brevital-anesthetized animals. All of the BaP/FeO exposed animals showed varying degrees of diffuse, acute bronchopneumonia, regardless of their anesthetic group, which were generally associated with areas of particle deposition. Focal epithelial hyperplasia and metaplasia were present in the trachea. "A few" animals died from acute purulent bronchopneumonia (*i.e.*, of infectious origin), and the number of animals succumbing was much greater in the DE exposed group than in the methoxyflurane-exposed group. None of the Brevital group displayed bronchopneumonia. Regarding neoplasms, the predominant tumor type in all segments of the respiratory tract was squamous cell carcinoma, and the most common site was the trachea, followed by bronchus. Multiple tumors in these areas were found in some animals. Adenocarcinomas and anaplastic carcinomas were also reported in the peripheral lung. The proportion of tumor bearing animals was highest in the DE exposed group (59/97, 61%), followed by the methoxyflurane group (52/94, 55%) and the Brevital group (41/95, 43%)[5]. With respect to the probability of observing a tumor at time of death in a BaP/FeO instilled animal, those animals exposed to DE were, in general, more likely to have tumors of the larynx, trachea, and bronchi at death for any point in the follow-up period than were hamsters anesthetized with either of the other agents. As for latency to the appearance of the first tumor-bearing animal, for tumors of the bronchi, hamsters exposed to DE developed tumors faster than did animals in the other two groups; for tumors of the trachea, the Brevital group had the shortest latency, the methoxyflurane the longest, with the DE group intermediate. For laryngeal and lung tumors, time to onset of first tumor was roughly the same among the groups. In summary, the authors concluded that the irritating properties of DE anesthesia were likely responsible for much of the increase in respiratory system cancer that was exhibited by those animals exposed to DE. Some responsibility was also attributed to increased infectious responses in the DE exposed, which were hypothesized to have contributed to retention of a sufficient dose of carcinogen at local sites in the lung. Thus, under conditions of this study, DE effectively acted as a promoter of respiratory system cancers initiated by another agent. An *in vitro* study using inverted intestinal sacs obtained from sacrificed rats (Capel and Williams, 1979) noted that absorption of the carcinogen dimethylnitrosamine was enhanced by exposure of the rats to DE prior to death. In the summary document produced by NEG/NIOSH (NEG/NIOSH, 1993), no data are cited which suggest either mutagenic or carcinogenic effects attributable to DE exposure.

The U.S Environmental Protection Agency (EPA) has published a chronic oral Reference Dose (RfD) on its IRIS database (IRIS, 1993). The RfD of 0.2 mg/kg-day is based on a No Observed Adverse Effect Level (NOAEL) of 500 mg/kg-day in a thirteen week oral gavage study in rats. The critical effect was considered to be depressed body weight, which was exhibited by both sexes at dose levels of 2000 mg/kg-day. Toxicity was marked at the highest dose (3500 mg/kg-day), and was characterized by mortality, body weight loss and decreased food consumption. Although histopathological examinations were carried out, they revealed no effects related to the administration of DE.

---

[5] The authors note, however, that the high early mortality and the short latency of tumors in the Brevital group should be borne in mind, and that a higher tumor incidence may have been observed had a greater number of animals survived for a longer period.

The American Conference of Governmental Industrial Hygienists (ACGIH) has set a Threshold Limit Value (TLV) for DE of 400 ppm (1210 mg/m^3) [based on an 8 hour time-weighted average (TWA) exposure scenario], and a Short Term Exposure Limit (STEL) of 500 ppm (1520 mg/m^3) (ACGIH, 1991). ACGIH has justified these concentrations by stating that they "should minimize the potential for demonstrable injury to health, irritation, or signs of narcosis among exposed workers". The STEL appears to be based on the comment of Cook (1945) that "the concentration of 500 ppm is suggested as the maximum allowable, not that appreciably more than this concentration cannot be regularly tolerated without injury to health, but to avoid irritation and complaint". The exact origin of the TWA concentration is more obscure, although it appears to be based on Henderson and Haggard's (1943) calculation that a 70 kg man inhaling 400 ppm could absorb a maximum of 1.25 g of DE, and that that individual's blood concentration would then be 0.018 g/L, a concentration "not associated with any signs of intoxication". ACGIH discusses an experimental study by Nelson and coworkers (1943), in which an average of 10 humans of mixed gender were exposed to one of several solvent vapors under study for 3-5 minutes in a 1200 ft^3 gas cabinet, in order to assess "unpleasant, not necessarily toxic, effects". Following exposure, each individual was asked to classify the vapor's effect on eyes, nose and throat as "no reaction", "slightly irritating" or "very irritating". Further, subjects were asked if they could work in an atmosphere at that concentration for an eight hour workday. The vapor concentration which the majority of subjects rejected as a working atmosphere was then considered to be objectionable. For DE, complaints of nasal irritation started at 200 ppm (606 mg/m^3), and 300 ppm (909 mg/m^3) was considered objectionable as a working atmosphere. DE was not reported as a eye or throat irritant by the majority at 200 ppm. While this study utilized, by design, inherently subjective endpoints, the study suggests that nasal irritation can occur at concentrations well below the established TLV. Both ACGIH and Cook have noted, however, that the subjects in Nelson *et al.*'s experiment would have "had no opportunity for occupational acclimatization"[6] (Cook, 1945), *i.e.*, they would not have developed the tolerance that has been observed in workers routinely exposed to DE (ACGIH, 1991; Henderson and Haggard, 1943). The Occupational Health and Safety Administration (OSHA) had attempted to adopt the ACGIH values as Permissible Exposure Limits (PELs). NIOSH (1994) has not recommended a TWA exposure limit, but has set an Immediately Dangerous to Life and Health (IDLH) concentration of 1900 ppm (5757 mg/m^3). In addition, NIOSH (1994) has questioned whether the TLV and STEL established by ACGIH and adopted by OSHA were adequate to protect workers from "recognized health hazards", which, in the case of DE, consisted of sensory irritation (Fed Register, 1989). This comment appears to be based on the findings of Nelson *et al.* (1943). In addition, Frantik *et al.* (1994), based on largely exploratory results from studies of acute neurotropic effects in rats and mice, have suggested that the STEL for DE "may not reliably protect workers from acute nervous depression"[7]. Despite these differing opinions, ACGIH, NIOSH and OSHA all agree that the critical effect of DE exposure in humans is ocular and upper respiratory irritation

---

[6] Indeed, Nelson *et al.* state explicitly in their paper that "no attempt was made to evaluate the effects of habituation...which in some cases would result in disappearance of unpleasant effects. For this reason it is not claimed that the figures provide a satisfactory basis for evaluation of workroom atmospheres".

[7] These authors conducted a series of "effect-air concentration" regressions based on observations of "inhibition of propagation and maintenance of the electrically evoked seizure discharge" determined for male rats exposed to various solvents by inhalation for 4 hours, and female mice similarly exposed for 2 hours. Their analyses suggested that solvents (including DE) with ceiling or STEL to Effective Concentration 10 (EC_{10}) ratios > 0.5 "have the limit too close to the acutely hazardous zone". The ratio listed by these authors for DE was 770:485 ppm.

(NIOSH, 1993; ACGIH, 1991; Fed Register, 1989), and that the available evidence suggests that this irritation can be expected to occur at a concentration somewhere between 200 and 400 ppm (606-1212 mg/m^3). The Commission of the European Communities (Elvestad *et al.*, 1993) concluded that "the available toxicity data concerning diethyl ether are incomplete and inadequate for setting occupational limit values".

Derivation of the ITSL: In choosing data for screening level development, preference is generally given to human epidemiologic data or chronic laboratory animal studies which can be used to derive a Reference Concentration (RfC). Such data were not found in our searches. It could be argued that Nelson *et al.* consitutes such data. However, the fact that 1) the study relied on subjective evaluations by a small number (n=10) of subjects, 2) that the means of subject selection (with respect to randomness and representativeness of the general population) were unspecified, and particularly, 3) that no sampling took place by which the nominal exposure concentrations reported could be objectively verified, render this study of insufficient quality for use in derivation of an RfC. When adequate data for RfC calculation are not available, next preference is given to oral data for calculation of a Reference Dose (RfD) if available data do not indicate that extrapolation from the oral to the inhalation route of exposure is inappropriate. In the case of DE, eye and upper airway irritation is the critical effect exhibited following inhalation exposure, suggesting portal-of-entry effects that may not be accurately accounted for by the use of oral data. The aforementioned suggestive evidence that the toxicity of DE in humans by inhalation may be somewhat different than its toxicity by ingestion would seem to argue against the use of oral data as well. Finally, human data is, in general, to be given precedence over animal data, and in the case of DE, the RfD is based on a rat gavage study of less than chronic duration. Thus, while the available data are far from ideal, the use of the oral RfD as the basis for calculating a screening level for DE seems questionable.

The next most appropriate alternative is an ITSL based upon an OEL. Given the unavailability of other inhalation data of sufficient quality for derivation of an RfC, and the inappropriateness of the use of oral data as noted above, the ACGIH-TLV is used here for the calculation of an ITSL for DE.

Per Rule 232(1)(c), part 55, of Act 451:

$$\textbf{ITSL} = \text{OEL} \times \frac{1}{100} = 1210\ mg/m^3 \times \frac{1}{100} = 12.1\ mg/m^3 \times \frac{1000\ \mu g}{1\ mg} = 12{,}100\ \mu g/m^3 \cong \mathbf{12{,}000\ \mu g/m^3}$$

where the factor of 1/100 is a safety factor to account for: 1) differences in susceptibility between the healthy, adult worker population as compared to the general population which may include individuals or subpopulations more sensitive to the effects of exposure to DE and 2) the difference in exposure duration for the worker population as opposed to the general population. The factor is derived as follows:

$$\text{Safety factor} = \frac{40\ \text{hours}}{168\ \text{hours}} \times \frac{30\ \text{years}}{70\ \text{years}} \times \frac{1}{10} = \frac{1}{100}$$

The first term adjusts for the difference between a 40 hour work week and the total hours in a week; the second factor adjusts for the difference between an assumed working life of 30 years and an assumed total lifespan of 70 years; and the third factor is a standard ten-fold uncertainty factor to extrapolate from the healthy worker to sensitive individuals in the general population. In the case of DE, this third factor would be

expected to account for the difference between the TLV and the concentration below it (606 mg/m3) at which Nelson's experimental subjects began to experience irritation[8]. Thus, the ITSL should be adequately protective of irritative effects in sensitive individuals in the general population, despite being based on the somewhat higher (1210 mg/m3) TLV concentration. However, it is acknowledged that the TLV is based upon old data and is less than ideally documented. Future review of the appropriateness of this screening level will be warranted as more recent data of better quality become available.

It should also be noted that conversation with at least one state (Texas) has found inhalation criteria below the ITSL calculated here, criteria based on the odor threshold for DE. Thus, it should be kept in mind that potential citizen complaints may not be unexpected in response to ambient concentrations of DE which are below this ITSL. It should also be noted that in evaluating odor impacts, AQD has traditionally looked at 10 minute averaging times in comparison to the odor threshold.

Consistent with 232(2)(a), since the used here is based on a time-weighted average, an **8 hour averaging** time applies.

[8] The assumption is made here that Nelson's experimental subjects were obtained from the general (rather than the worker) population, although this cannot be verified with the information available, since description of the origin and characteristics of the study group is lacking.

REFERENCES

ACGIH (1991). Ethyl ether (60-29-7). *In*: Documentation of Threshold Limit Values and Biological Exposure Indices, American Conference of Governmental Industrial Hygienists, Cincinnati, pp. 631-632.

Amor, A.J. (1950). The toxicity of solvents. *Paint Manufac* **20**(2):53-58.

Anonymous (1915). Queries and minor notes; Ether drinking. *J Amer Med Assoc* **64**:168 [cited in Bartholomew, 1962].

Bartholomew, A.A. (1962). Two cases of ether addiction/habituation. *Med J Austr* **49**:550-553.

Baselt, R.C. (1980). Ether, pp. 134-136. *In*: Biological Monitoring Methods for Industrial Chemicals. Biomedical Publications, Davis, CA, 301 pp.

Bredeman, W. (1950). Polyneuritis nach Miss bruch von Hoffman Strophen. *Ärztl Wschr* **5**:559 [cited in Bartholomew, 1962].

Capel, I.D. and Williams, D.C. (1979). Factors influencing carcinogen absorption *in vitro*. *IRCS Med Sci: Libr Compend* **7**(4):214.

Chenoweth, M.B., Leong, B.K.J., Sparschu, G.L. and Torkelson, T.R. (1972). Toxicities of methoxyflurane, halothane and diethyl ether in laboratory animals on repeated inhalation at subanesthetic concentrations. *In*: Cellular Biology and Toxicity of Anesthetics; proceedings of a research symposium held in Seattle, May 11-12, 1970, pp. 275-285. Williams & Wilkins, Baltimore, 328 pp.

Cook, W.A. (1945). Maximum allowable concentrations of industrial atmospheric contaminants. *Indus Med* **14**(11):936-946.

Dinwiddie, S.H. (1994). Abuse of inhalants: A review. *Addiction* **89**(8):925-939.

Elvestad, K., Hansen, L.E. and Jelnes, J.E. (1993). Occupational exposure limits -- criteria document for diethyl ether. Department of Environmental Toxicology, Danish Technological Institute, Taastrup, Denmark, for the Commission of the European Communities, Luxembourg. Commission of the European Communities, Directorate-General, Employment, Industrial Relations and Social Affairs, Document # EUR 14384, 20 pp.

Enhorning , G., Pototschnik, R., Possmayer, F. and Burgoyne, R. (1986). Pulmonary surfactant films affected by solvent vapors. *Anesth Analgesia* **65**(12):1275-1280.

Farman, J.V. (1981). Some long established agents -- a contemporary review. *Br J Anaesth* **53**(Suppl 1):3s-9s.

Fed Register (1989). *Federal Register* **54**(12):2461 (1/19/89).

Flanagan, R.J. and Ives, R.J. (1994). Volatile substance abuse. *Bull Narcotics* **46**(2):49-78.

Frantik, E., Hornychova, M. and Horvath, M. (1994). Relative acute neurotoxicity of solvents: Isoeffective air concentration of 48 compounds evaluated in rats and mice. *Environ Res* **66**(2):173-185.

Gargas, M.L., Andersen, M.E. and Clewell, H.J. (1986). A physiologically based simulation approach for determining metabolic constants from gas uptake data. *Toxicol Appl Pharmacol* **86**(3):341-352.

Glowa, J.R. (1993). Behavioral and neuroendocrine effects of diethyl ether exposure in the mouse. *Neurotoxicol Teratol* **15**(4):215-221.

Hawley, G.G. (1981). The Condensed Chemical Dictionary. Tenth Ed. Van Nostrand Reinhold Company, New York, p. 435.

Henderson, Y. and Haggard, H.W. (1943). Volatile drugs and substances: Ethyl and isopropyl ethers. *In*: Noxious Gases and the Principles of Respiration Influencing Their Action, Second Edition. ACS Monograph Series. Reinhold Publishing, New York, pp. 194-195.

Henry, M.C. and Port, C.D. (1978). Effect of anesthetic agent on lung tumor induction in hamsters given benzo[a]pyrene-ferric oxide. *J Natl Cancer Inst U.S.* **61**(5):1221-1226.

IARC (1976). *Cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general consideration of volatile anaesthetics.* Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 11, pp. 285-290. International Agency for Research on Cancer, Lyon.

Infante, P.F. and Tsongas, T.A. (1981). 24. Anesthetic gases and pregnancy: A review of evidence for an occupational hazard, pp. 287-294. *In*: Occupational Hazards and Reproduction (Hemminski, K. Sorsa, M. and Vainio, H., Eds.) Hemisphere Publishing, Washington D.C., 333 pp.

IRIS (1993). Ethyl ether (60-29-7). Integrated Risk Information System, U.S. Environmental Protection Agency.

Kirwin, C.J. and Galvin, J.B. (1993). 2.2. Diethyl Ether. *In*: Patty's Industrial Hygiene and Toxicology, 4th Ed. (Clayton, G.D and Clayton F.E., Eds.), Volume II, Part A, Chapter Eight: Ethers. John Wiley and Sons, Inc., New York, pp. 459-463.

Kunisaki, T.A. and Augenstein, W.L. (1994). Drug- and toxin-induced seizures. *Emerg Med Clin N Amer* **12**(4):1027-1056.

Lam, C-W., Galen, T.J., Boyd, J.F. and Pierson, D.L. (1990). Mechanism of transport and distribution of organic solvents in blood. *Toxicol App Pharmacol* **104**(1):117-129.

Merck (1983). The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals, (Windholz, M., Ed.) Tenth Ed. Merck and Company, Rahway, N.J., p. 551.

Moeschlin, S. (1986). Klinik und Therapie der Vergiftungen. Georg Thieme Verlag, Stuttgart, p. 337 [cited in NEG/NIOSH, 1993].

NEG/NIOSH (1993). NEG and NIOSH Basis for an Occupational Health Standard: Ethyl Ether. Nordic Expert Group for Documentation of Occupational Exposure Limits, and National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Public Health Service, U.S. Department of Health and Human Services. DHHS (NIOSH) publication #93-103, 39 pp. [Originally published as Arvidson, B. (1992), *Arbete Och Hälsa* **1992**:30].

Nelson, K.W., Ege, J.F, Ross, M., Woodman, L.E. and Silverman, L. (1943). Sensory response to certain industrial solvent vapors. *J Ind Hyg Toxicol* **25**:282-285.

NIOSH (1994). NIOSH Pocket Guide to Chemical Hazards. National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Public Health Service, U.S. Department of Health and Human Services. DHHS (NIOSH) publication #94-116, p. 76.

Perez-Llamas, F., Zamora, S., Rosique, M.J. and Sastre, J.F. (1992). Effects of inhalation of ethyl-ether on glycemia and on some variables of intermediate metabolism in rats. *Arch Int Physiol Biochim Biophys* **100**(5):335-337.

Poulin, P. and Krishnan, K. A biologically-based algorithm for predicting human tissue:blood partition coefficients of organic chemicals. *Hum Exp Toxicol* **14**(3):273-280.

RTECS (1996). 1,1'-oxy*bis*-ethane (60-29-7). *In*: Registry of Toxic Effects and Chemical Substances Database. National Institute for Occupational Safety and Health, Public Health Service, Centers for Disease Control, U.S. Department of Health and Human Services, and Canadian Centre for Occupational Safety and Health.

Shelley, M.L., Andersen, M.E. and Fisher, J.W. (1989). A risk assessment approach for nursing infants exposed to volatile organics through the mother's occupational inhalation exposure. *Appl Ind Hyg* **4**(1):21-26.

Smith, B.E., Gaub, M.L. and Lehrer, S.B. (1968). Teratogenic effects of diethyl ether in the chick embryo. *In*: Toxicity of Anesthetics: Proceedings of a research symposium held in Seattle, May 12-13, 1967 (Fink, B.R., Ed.). Williams and Wilkins, Baltimore, 332 pp.

Schwetz, B.A. and Becker, B.A. (1971). Comparison of the lethality of inhaled diethyl ether in neonatal and adult rats. *Toxicol App Pharmacol* **18**(3):703-706.

Taskinen, H., Kyyrönen, P., Hemminki, K., Hoikkala, M., Lajunen, K. and Lindbohm, M-L. (1994). Laboratory work and pregnancy outcome. *J Occup Med* **36**(3):311-319.

Van Dyke, R.A. and Chenoweth, M.B. (1965). Metabolism of volatile anesthetics: A review. *Anesthesiology* **26**:348 [cited in Chenoweth *et al.*, 1972].

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd Ed. Van Nostrand Reinhold Company, New York, p. 656-657.

Watanabe, A. and Kuwabara, Y. (1994). Hyperammonemia induced in rats by inhalation anesthesia with ether. *Res Exp Med (Berl)* **194**(3):157-164.

DO:slb
cc: Paul Schleusener, Permits Unit, AQD