MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

July 9, 1996

TO: File for Glycerin (CAS # 56-81-5)

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

SUBJECT: Initial Threshold Screening Level (ITSL) for glycerin

The ITSL for glycerin is 100 $\mu g/m^3$ based on an 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 July 31, 1995), CESARS, Handbook of Environmental Data on Organic Chemicals, Patty's Industrial Hygiene and Toxicology, Merck Index and Condensed Chemical Dictionary.

Glycerin (glycerol) is widely used in the manufacture of plastics, cosmetics, confectioneries, explosives and other chemicals, and as a dispersant in pharmaceutical preparations (ACGIH, 1992). It also occurs in processed foods (Kern, 1980), and has been generally recognized as safe (GRAS) since 1959 for incorporation as a general purpose food additive (Renne *et al.*, 1992).

Clinically, glycerol is used as an osmotic dehydrating agent to draw edema fluid out of the CNS and also to reduce intraocular pressure (*e.g.*, as a therapeutic agent in the treatment of glaucoma). These therapeutic uses have been reviewed by Tourtellotte *et al* (1972) and Frank *et al* (1981). It can be administered both orally and intravenously. It is also considered nutritive, since glycerol is a metabolic intermediate in normal humans. With respect to mechanism of action, glycerol is filtered at the glomerulus and almost completely reabsorbed at the tubular level, until serum concentrations exceed 0.15 mg/ml. At that point, it is no longer reabsorbed, and accumulates in the urine, causing osmotic diuresis roughly equivalent to the amount administered. "The absolute increase in serum osmolality required to produce significant cerebral and intraocular dehydration is not entirely clear." Decreases in intracranial pressure after glycerol administration to nephrectomized rats suggest that part of the therapeutic effect is extrarenal; effects are speculated to be due to alterations in brain metabolism and/or perfusion. Decline in intraocular (IOP) and intracerebral (ICP) pressure occurs within 10 to 30 minutes whether administration is oral or *i.v.*, and in humans with relatively intact blood-brain barriers, oral glycerol is generally effective in lowering ICP for 2-3 hours. Orally administered, glycerol reaches peak plasma concentrations in 60-90 minutes, reaching 1.45 mg/ml after a single 1-1.27 g/kg bw dose. The therapeutic dose for CNS dehydration listed by Tourtellotte *et al.* is 1 g/kg every 6 hours. Elimination half life in humans is approximately 30-45 minutes. One study involving "10 patients with normal liver function" reported a mean clearance of 2.17 ml/kg/minute. Metabolism is largely hepatic, so patients with significant liver disease would be expected to have

lower clearance, and there does not appear to be a significant first-pass effect. Some animal results extrapolated to humans have suggested that near equivalent doses orally or *i.v.* may produce the same amount of therapeutic effect. Human data suggest glycerol clearance is constant over a dose range of 0.38-0.88 g/kg/hr, whereas canine findings reflected a process saturable at a dose of 0.32 g/kg/hr. A group of fourteen college students were given 1.3 to 2.2 g/kg glycerol orally in orange juice with each meal for 50 days, and no pathologic reactions were noted. Adverse reactions in people include pulmonary edema (Almog *et al*, 1986), renal damage, hyperglycemia, hyperosmolality, and most frequently, hemolysis accompanied by hemoglobinuria. Of these, only pulmonary edema, hyperglycemia and hyperosmolality are observed with oral administration, and "hyperglycemia is generally not a problem, except in diabetics." The mechanism of the hemolysis appears to be purely osmotic, rather than cytotoxic; glycerol freely crosses the erythrocyte membrane, where it draws water. The intracellular compartment swells with fluid and when the elastic limit of the membrane is exceeded, the cell lyses. Effects which have been observed in animals but which are of questionable human relevance include muscle irritability, relaxation of the gallbladder sphincter, and increased force and amplitude of intestinal contractions. In "animals", single 8-15 g/kg doses produced restlessness and diminished activity followed by an increasing pulse rate, vomiting, occasional biting movements, cyanosis, tremor, diuresis, some loss in equilibrium, severe clonic convulsions, and even death. However, in man this sequence has never been observed; a 2.5 yr. old child ingested 300 g (23 g/kg) and went into coma but ultimately recovered completely. One fatality has been reported in the German literature, but the dose and mode of administration were not known. Rare fatal reports in the literature seem to have followed irreversible renal damage, but the causal relationship to glycerol .is difficult to establish.

The pharmacokinetics of glycerin taken orally by humans was investigated by Sommer *et al* (1993) in a group of ten healthy subjects, age 23-47 yrs. Each subject received a single dose of glycerol at 1.2 g/kg bw. Intestinal absorption was rapid, with maximal serum concentrations being reached 1-2 hours after ingestion. If full intestinal absorption is assumed, total body clearance was 0.18-0.26 L/hr/kg. Kinetics did not indicate a linear dose response relationship. Terminal elimination half-life ranged from 0.61-1.18 hours. In all subjects glycerin serum concentrations were high enough to induce increases of serum osmolality of at least 10 mOsmol/kg, but no signs of hemolysis or hemodilution were observed.

With respect to Occupational Exposure Limits (OELs), the American Conference of Governmental Industrial Hygienists (ACGIH) has established a time-weighted average Threshold Limit Value (TLV) of 10 mg/m^3 as total particulate (ACGIH, 1992). ACGIH notes that "glycerin mist is considered a 'nuisance' particulate which seems to have little adverse effect on the lung and does not produce significant organic disease or toxic effects when exposures are kept under reasonable control." The Occupational Safety and Health Administration (OSHA) has set Permissible Exposure Limits (PELs) of 10 mg/m^3 total particulate, and 5 mg/m^3 respirable particulate. The National Institute for Occupational Safety and Health (NIOSH) has not set an OEL for glycerol; they did not concur with OSHA's limits, citing concerns over possible reproductive effects (arrested spermatogenesis) reported in rats (Wiebe and Barr, 1984) and squirrel monkeys (Wiebe *et al.*, 1989). However, the route of administration of glycerin in both these studies was intratesticular injection, a route of doubtful relevance to inhalation exposures.

Renne and coworkers (1992) have published the results of a subchronic inhalation study, sponsored by the R.J. Reynolds Tobacco Company, in which cesarean delivered, barrier-

maintained, Sprague-Dawley derived (Crl:CD) rats were exposed, nose only, to aerosolized glycerol for 6 hours/day, 5 days/week, for 13 consecutive weeks. Fifteen rats/sex/grp were exposed to target concentrations of 0 (sham exposed), 0.033, 0.165 and 0.660 mg/L for the course of the study. A number of steps were taken to assure control of temporal and spatial heterogeneity and to characterize particle size and impact analysis. These included hourly measurement of aerosol concentrations in each group during exposure at each of the separate exposure ports, and weekly determinations of aerodynamic particle size using Mercer cascade impactors. Animals were quarantined, subjected to health screening, and spent several hours being acclimated to the restraint system associated with the nose-only exposure apparatus. When not being exposed, the animals were individually housed and had *ad libitum* access to both lab chow and water. Twice daily the animals were monitored for clinical signs of toxicity, morbidity and mortality; all rats were weighed at weekly intervals, and diet consumption was measured weekly during one 17 hour nonexposure period. Just prior to terminal sacrifice, blood samples were obtained under CO_2 anesthesia for hematology and serum chemistry tests. All rats on the study were subjected to complete gross necropsy; the entire respiratory tract (including the nasal cavity) and associated lymph nodes, a complete set of 40 other tissues, and all gross lesions were fixed for histopathological exam. In addition, lungs from selected rats in the control and the 0.66 mg/L exposure groups (3 of each sex/grp) were obtained from animals euthanized after 10 weeks of exposure and examined ultrastructurally via transmission electron microscopy (TEM). At the terminal necropsy, lungs from 3 randomly selected rats of each sex from each exposure group were also prepared for TEM; selected samples from the high exposure and control groups were examined. Body weights/gains, food consumption, organ:body and organ:brain weight ratios and clinical pathology data were stratified on sex and exposure group and subjected to ANOVA, and if the results were significant, multiple comparisons of means were made using the least significant difference criterion. Results were considered significant at a level of $p < 0.05$, two tailed. Incidence and severity of lesions between each exposure level and controls were carried out using contingency table analysis.

Actual concentrations generated by the aerosolizing apparatus were quite close to targets, with mean concentrations of 0, 0.033, 0.167 and 0.662 mg/L (based on 108 samples per exposure level). The authors report corresponding concentrations in mg/m^3 of 0, 33, 167 and 660 mg/m^3. Mass median aerodynamic diameters (mean ± geometric S.D.) in the three exposed groups were 1.09 ± 1.9, 1.49 ± 1.69 and 1.61 ± 1.75 mm in the low, mid and high exposure groups respectively, based on 13 samples each. As the mean MMAD for all groups was below 2 mm, generated aerosols for all groups were within the respirable range of aerosols in the rat. No clinical signs attributable to glycerol exposures were noted during any of the twice daily or detailed monthly observations. No mortality is reported, although the possibility that some occurred cannot be excluded, since the only summary tables published show sample numbers per group ranging from 21 in the high dose group to 25 in the sham controls, clearly less than the 30 per group expected given the experimental design and 100% survival to termination[1]. Since the authors make reference to the fact that "suitable sections through the base of the epiglottis" were examined for less than the full complement of 30 animals in each group, it is possible that the numbers reported in this table were restricted only because of sample availability and not because of mortality. However, the reason for the decreased numbers reported is not

[1] In an earlier two week study by the same authors with the same exposure apparatus, 4 of 80 rats (5%) "died while confined in the restraining tubes during exposure." Given the restrictive nature of the nose-only exposure apparatus, it seems plausible that stress to the animals could have played a role in the deaths reported, but this is purely speculative, and relevant data are not reported.

stated with sufficient clarity to allow a definitive conclusion to be made as to the fate of the missing animals. "Statistical analysis of group means for body and organ weight data, organ weight:terminal body weight ratios, organ weight:brain weight ratios and feed consumption showed some significant differences among groups, but these differences lacked consistency or exposure concentration-response relationships and were interpreted as having no biological significance." There were no statistically significant differences in hematological parameters between any of the groups or either sex. The only significant differences in the chemistry parameters were increased triglyceride concentrations compared to controls in the low and mid, but not high, dose males; there were no differences in any of the female groups. The authors considered these findings neither related to glycerol exposure nor biologically significant. There were no gross lesions attributable to glycerol exposure. Minimal squamous metaplasia of the basal epiglottic epithelium was observed in 10 of 21 rats in the high dose group for which suitable histologic sections were available; a single rat from the high dose group had histopathologic evidence of mild squamous metaplasia. Together, these 11 animals provided a significantly increased incidence of squamous metaplasia compared to controls ($p = 0.01$ by Fisher's Exact Test). There were no statistically significant exposure-related effects at the mid or low exposure concentrations, although there was some evidence of a dose-response relation with regard to epiglottic squamous metaplasia; incidences were 2/25, 1/19, 4/20 and 11/21 in the 0, 33, 167 and 660 mg/m^3 groups, respectively. In non-respiratory tissues, there was a low incidence of histopathologic lesions in all groups, including controls, but none were considered attributable to exposure. There were no differences in the morphology of Clara cells of glycerol exposed and control rats. "The proliferation of SER (presumably, smooth endoplasmic reticulum) and the abnormalities in shape of Clara cell mitochondria, reported in glycerol-exposed ddY mice by Kitamura *et al* (1987) [below], were not observed in this study. These authors concluded that the no-observed-effect concentration (NOEL) in this study was 0.167 mg glycerol/L (167 mg/m^3), and felt that the statistically elevated incidence of squamous metaplasia noted in the high dose group was an adaptive, rather than adverse, effect.

In a separate paper (Burger *et al*, 1989), this same group of researchers discussed the significance of squamous metaplasia, and other cellular morphological alterations of the respiratory tract, as manifestations of physiological adaptation, as opposed to overt toxicity. The argument was advanced that minimal squamous metaplasia, such as that found in Renne *et al*, "...in laboratory rats exposed to aerosolized glycerol...appear to represent adaptive rather than toxic changes because of the following factors: 1) the squamous metaplasia is focal and minimal; 2) there is a lack of observed keratinization; 3) it was seen in rats but not in hamsters or mice and is only in a very specific area of the larynx; 4) it resembles the focal squamous metaplasia occasionally observed in control rats in inhalation studies; and 5) it is well differentiated and lacks signs of atypia, dysplasia, and dyskeratinization." While this paper is well researched, and copiously documented with histopathologic sections, it is perhaps notable that many of the arguments for adaptation vs. toxic effect which are applied to glycerol inhalation are also applied by these authors to the effects of cigarette smoke inhalation.

A series of reports by Japanese workers (Nagahara *et al.*, 1990*b*; Kitamura *et al.*, 1987; Inayama, 1986; Inayama *et al.*, 1986) have investigated possible carcinogenic or promoting effects of glycerol on lung tumors in male ddY mice initiated by 4-nitroquinoline-1-oxide (4NQO) or urethan (Nagahara *et al.*, 1990*a*). These investigators found statistically significant elevated numbers of pulmonary tumors in mice given a single subcutaneous or intraperitoneal injection of 4NQO and maintained on a 5% glycerol solution as drinking water for periods of four to thirty weeks, in comparison

to controls given 4NQO but not glycerol. Tumors were observed grossly in excised lungs with a dissecting microscope. No such effects were noted in the urethan treated mice. Other experiments by this group (Kitamura *et al.*, 1987) lead them to believe that glycerol was altering the function of alveolar Clara cells, and that this might account for the promoting activity they observed. A separate set of workers (Witschi *et al.*, 1989) attempted to replicate these findings in several strains of both rats and mice, and with other tumor initiators (urethane and 3-methylcholanthrene). In their experiments, the effects of glycerol were variable, but in the majority of cases glycerol failed to enhance lung tumor development in mice. Analysis of cell kinetics did not demonstrate the proliferative response in alveolar and bronchiolar cells found by the Japanese investigators, nor did glycerol increase the spontaneous incidence of liver tumors or neoplastic hepatocellular foci in mice or rats. Moreover, in no study by either group of investigators was glycerol by itself shown to increase the incidence of tumors compared to controls. The available data do not support consideration of glycerol as a carcinogen.

The Inhalation Reference Concentration (RfC) is given first preference as data on which to base an ITSL. This concentration can be used without modification when it has been derived previously by EPA. Lacking that, data from well-conducted epidemiological studies in humans or inhalation bioassays in laboratory animals may also be used to derive an RfC. While epidemiological studies of humans exposed to glycerin by inhalation are unavailable, the study of Renne and coworkers (1992) incorporated the inhalation route of exposure, and is of sufficient length (thirteen weeks) for use in RfC development (EPA, 1994; Table 4-1, p. 4-3). Unfortunately, the failure of Renne *et al* to explicitly account for the fate of all of the animals in the study casts doubt on the quality of an otherwise well-conducted experiment. Nonetheless, an RfC based on the Renne study is derived below for comparison with a screening level based upon the ACGIH-TLV, as these two data sources were the best located during the search of the toxicological literature. Since this study recorded NOAELs at multiple dose response levels in the absence of additional inhalation data, the highest NOAEL, *i.e.*, 167 mg/m^3, would be used to drive the RfC. Note that, in contrast to the conclusions of Renne *et al*, the significantly elevated incidence of squamous metaplasia observed in the high dose group (660 mg/m^3) is considered here to be an adverse, rather than adaptive, effect, and that dose level is considered a Lowest Observed Adverse Effect Level (LOAEL).

Human Equivalent Concentration (HEC) Calculation:

a) Dose adjustment is necessary to account for discontinuous exposure regimens used in the key study. Per EPA (1994), section 4.3.2, p. 4-21:

$$NOAEL_{[ADJ]}\ (mg/m^3) = 167\ mg/m^3 \times \frac{6\ hrs/day}{24\ hrs/day} \times \frac{5\ days/week}{7\ days/week}$$

$$= 167\ mg/m^3 \times 0.25 \times 0.71 = 29.8\ mg/m^3$$

b) Since the critical toxic action of glycerol manifest in Renne et al. (1992) was upper respiratory irritation, the HEC is determined assuming respiratory tract effects. Under the conditions of the study, exposure-related histopathological lesions were limited to the base of the epiglottis; calculations based on an

extrathoracic (ET) effect are thus appropriate[2]. Consequently (section 4.3.5, p. 4-30),

$$NOAEL_{[HEC]}\,(mg/m^3) = NOAEL_{[ADJ]}\,(mg/m^3) \times RDDR_{(ET)}$$

$$NOAEL_{[HEC]}\,(mg/m^3) = NOAEL_{[ADJ]}\,(mg/m^3) \times \frac{(RDD_{ET})_{animal}}{(RDD_{ET})_{human}}$$

where $(RDD_{ET})_{animal}/(RDD_{ET})_{human}$ is the ratio of Regional Deposited Doses (RDDR) in the test animal species (rat) to that in humans for the region of interest (here, the extrathoracic region) for the toxic effect. The RDDR used here is obtained from output of the C computer program (rddr.exe) included as a supplement to EPA (1994); the value corresponds to the MMAD of 1.49 and the geometric standard deviation (σ_g) of 1.69 reported by Renne *et al.* (1992, Table 7, p. 105), based on thirteen samples obtained with cascade impactors during animal exposure in the 167 mg/m^3 exposure group. This σ_g (> 1.3) characterizes the particles as polydisperse, and indicates the use of the computer-generated RDDR, rather than a hand-calculated RDDR), as appropriate in this instance (per p. 4-32)[3]. Copies of the output tables from rddr.exe follow the reference section of this screening level derivation.

So,

$$NOAEL_{[HEC]}\,(mg/m^3) = NOAEL_{[ADJ]}\,(mg/m^3) \times RDDR_{(ET)}$$

$$= 29.8\ mg/m^3 \times 0.235$$

$$= 7.0\ mg/m^3$$

Inhalation Reference Concentration (RfC) calculation:

Per EPA (1994), section 4.3.9.1, p. 4-74:

$$RfC = NOAEL_{[HEC]}/(UF \times MF)$$

$$= \frac{7\ mg/m^3}{([10 \times 10 \times 3] \times 1)} = 0.023\ mg/m^3 \times \frac{1000\ \mu g}{1\ mg} = 23.3\ \mu g/m^3$$

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[2] It should be noted that EPA (1994) states (p. 4-30) that this approach is "limited at this time to relatively insoluble and nonhygroscopic particles;" glycerol is both water soluble and hygroscopic (Merck, 1983). While this would seem to render the approach inappropriate for determination of the ITSL, EPA also notes (p. 4-41) that "dosimetric adjustment by the default insoluble (nonhygroscopic) empirical deposition equations is recommended as a conservative default for the hydroscopic particles, pending modification by the elucidation of hygroscopic models."

[3] The RDDR stated above is the mean of the RDDRs generated by the C program for male and female Sprague-Dawley rats calculated separately. This is considered appropriate since the histopathologic lesions that were the critical effects in Renne *et al.* were not enumerated by sex by the authors. Consequently, it is not possible to determine if one sex or the other exhibited the preponderance of the lesions and thus should be considered more sensitive to the effects of glycerol exposure under the conditions of the study.

where the total UF of 300 is composed of: 1) 2 10-fold uncertainty factors to account for extrapolation from average healthy humans to sensitive humans, and extrapolation from the subchronic NOAEL of the Renne *et al.* study to a chronic NOAEL (since no longer term studies were available), and; 2) a 3-fold uncertainty factor for interspecies extrapolation from rats to humans. This uncertainty factor is decreased from the default value of 10 in recognition of the fact that the inhalation dosimetry calculations above account for the uncertainty attributable to disposition variability in the interspecies extrapolation (EPA, 1994, p. 4-78). The MF assumes the default value of 1.

Derivation of the ITSL:

The most desirable alternative to an ITSL based on an inhalation RfC is a screening level based on an oral Reference Dose (RfD). In this case, however, the results of Renne and coworkers suggest that exposure to glycerol *via* the inhalation route elicits portal-of-entry effects (basal epiglottic epithelial squamous metaplasia), suggesting that an ITSL based on oral data may be inappropriate for assessment of risks due to inhalation exposures.

The next most appropriate alternative is an ITSL based upon an OEL. Given the inadequate accounting of test animals in the Renne *et al.* (1992) study, 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 for the calculation of an ITSL for glycerol. Per Rule 232(1)(c) of Act 348:

$$\textbf{ITSL} = \text{OEL} \times \frac{1}{100} = 10\ \text{mg/m}^3 \times \frac{1}{100} = 0.1\ \text{mg/m}^3 \times \frac{1000\ \mu\text{g}}{1\ \text{mg}} = \textbf{100}\ \boldsymbol{\mu\text{g/m}^3}$$

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 glycerol 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.

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

By way of comparison, it should be noted that a screening level derived using the Renne study, once converted to the concentration equivalent for an 8 hour averaging time *via* dilution factors, would be 42 $\mu g/m^3$, which differs from the ITSL derived using the TLV by less than a factor of three. Hence, the two methods result in screening levels which are not inconsistent with each other.

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Table 1: Regional deposited dose ratios, males (data from Renne *et al.*, 1992).

MMAD = 1.49
Sigma g = 1.69

SPECIES	Body weight(g)	VE(ml)	Extrathoracic SA(cm^2)	dep	Tracheobronchial SA(cm^2)	dep	Pulmonary SA(m^2)	dep
rat	267	189.8	15.000	0.390	22.500	0.070	0.340	0.079
human	70000	13800.0	200.000	0.255	3200.000	0.065	54.000	0.279
RATIO	0.004	0.014	0.075	1.526	0.007	1.076	0.006	0.282
RDDR			0.280		2.105		0.615	

	Thoracic SA(m^2)	dep	Total RT SA(m^2)	dep	Extrarespiratory BW(g)	dep
rat	0.342	0.149	0.344	0.539	267	0.539
human	54.320	0.125	54.340	0.599	70000	0.599
RATIO	0.006	1.188	0.006	0.898	0.004	0.898
RDDR	0.943		1.953		3.239	

V. 2.3

Table 2: Regional deposited dose ratios, females (data from Renne *et al.*, 1992).

MMAD = 1.49
Sigma g = 1.69

SPECIES	Body weight(g)	VE(ml)	Extrathoracic SA(cm^2)	dep	Tracheobronchial SA(cm^2)	dep	Pulmonary SA(m^2)	dep
rat	204	152.2	15.000	0.330	22.500	0.082	0.340	0.099
human	70000	13800.0	200.000	0.255	3200.000	0.065	54.000	0.279
RATIO	0.003	0.011	0.075	1.293	0.007	1.252	0.006	0.354
RDDR			0.190		1.963		0.620	

	Thoracic SA(m^2)	dep	Total RT SA(m^2)	dep	Extrarespiratory BW(g)	dep
rat	0.342	0.180	0.344	0.510	204	0.510
human	54.320	0.125	54.340	0.599	70000	0.599
RATIO	0.006	1.440	0.006	0.852	0.003	0.852
RDDR						