MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

February 8, 1995

TO: File for Cyclopentane (CAS # 287-92-3)

FROM: Dan O'Brien

SUBJECT: Initial Threshold Screening Level for Cyclopentane

The initial threshold screening level (ITSL) for cyclopentane is 17,200 $\mu g/m^3$ 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 -February 3, 1995), CESARS, Handbook of Environmental Data on Organic Chemicals, Patty's Industrial Hygiene and Toxicology, Merck Index and Condensed Chemical Dictionary.

Cyclopentane occurs infrequently in nature, due to its instability. It is produced in petroleum refining processes, and is found as an impurity in technical grade hexane. It is commonly used for cracking aromatics, and commercially, to produce a variety of pharmaceuticals and insecticides (Cavender, 1994). It is also found in petroleum ether and other commercial solvents that are used as a fuel, in fat and wax extraction, in paints, and in the shoe industry (ACGIH, 1991). Due to the quite limited use of cyclopentane in industry, no major animal toxicity studies have been published. What little data is available appears to be conflicting with respect to general toxic severity. While von Oettingen (1940) records minimal narcosis, hyporeflexia and lethality in mice all occurring at a concentration of 38.3 ppm (110 mg/m^3; length/frequency of exposure(s) not noted), a more recent study by Kimmerle and Thyssen (1975) records no effects in rats of either sex exposed to cyclopentane 6 hrs/day for 3 weeks by inhalation at concentrations up 1139 ppm (3269 mg/m^3). The same authors report decreased body weight gains in females exposed 6 hrs/day to 8110 ppm (23,276 mg/m^3) with longer exposure durations of 12 weeks. While such a difference in species sensitivity is certainly possible, the lack of other studies with which to corroborate such a marked disparity cast some doubt on the validity of one or both of these studies, and on their usefulness in deriving an ITSL.

Some human toxicity and exposure data is available in the form of occupational studies and exposure limits. Kimmerle and Thyssen (1975) report exposure concentrations of 10 to 15 ppm (29 to 43 mg/m^3) to be "tolerable" for humans. The National Institute of Occupational Safety and Health (NIOSH), the Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH) have all agreed upon an Occupational Exposure Limit (OEL) of 600 ppm (1720 mg/m^3). While the health issues under consideration in setting this OEL appear to be adequately documented, an explicit

justification/rationale for setting the OEL at this particular concentration was not found. The extensive justification which accompanies the rule setting OSHA Permissible Exposure Limits (PELs) (Federal Register, 1989*b*) categorizes cyclopentane with chemicals whose primary adverse effect is narcosis. OSHA notes that "occupational exposure to cyclopentane poses a significant risk of irritation and narcosis, which constitute material impairments of health that occur at levels somewhat above the PEL established in the final rule". NIOSH, in its invited review comments prior to the rulemaking, "concurred with this limit", although it is noted elsewhere in the rulemaking (Federal Register, 1989*a*) that NIOSH also commented that "analytical methods [for cyclopentane] would benefit from additional analysis". The concurrence of NIOSH with this PEL should be viewed along side their lack of agreement with the PEL for *n*-pentane (Federal Register, 1989b), the compound upon which ACGIH based its TLV for cyclopentane (ACGIH, 1991). While OSHA does not explicitly state in the cyclopentane rulemaking that the ACGIH-TLV is the basis for their PEL, the fact that the two OELs are set at the same concentration seems more than coincidental.

The reason for NIOSH's disagreement with the TLV for *n*-pentane lies in the fact that NIOSH's Recommended Exposure Limit (REL) for all of the C_{5-8} aliphatic alkanes assumes the peripheral neuropathy produced by *n*-hexane exposure can be caused by other alkanes (or mixtures of alkanes) and their isomers (Federal Register, 1989*a*). NIOSH's justification appears to be based on studies where neuropathies resulted from exposure to mixed alkanes (Abbritti *et al.*, 1976; Gaultier *et al.*, 1973). While neuropathies have resulted from exposure to solvents *containing* cyclopentane or *n*-pentane, in neither of these studies were the authors able to demonstrate a causal relationship between the occurrence of nervous symptoms and exclusive exposure to the pentanes. Any component alkane present in the mixture could potentially have accounted for all or part of the neuropathy observed, a point stated unequivocally by the investigators of both studies. All of the studied solvents contained *n*-hexane, and since the ability of hexane to produce neuropathy is well established, it would appear to be the agent most likely responsible for the clinical signs observed in these studies, although the possibility that other alkanes were wholly or partially responsible cannot be excluded. OSHA makes a convincing case that *n*-hexane is the exclusive causal alkane (Federal Register, 1989*a*), and that there is little justification for regulating pentane and the other C_{5-8} alkanes with the stringency appropriate for hexane.

Careful reading of the epidemiological study of Abbritti *et al.* (1976), tends to support OSHA's position. These authors collected seven samples of solvents and glues used in five of 72 shoe factories where 20 of 122 cases of polyneuropathy were recorded, and analyzed them for the presence and quantity of alkanes. *N*-hexane was present in all samples taken from all sites, in proportions ranging from 15 - 72 % of the solvent composition by weight; the mean proportion was 51%. By contrast, cyclopentane and *n*-pentane were present in only four of the samples, in proportions ranging from 0.3 - 4.2 % by weight (median = 0.42 %) for cyclopentane, and from traces to 44.9 % by weight (median = 0.3 %) for *n*-pentane. Assuming that the solvents/glues and factories sampled were representative of the whole population of effected workplaces, and that the individual cases of neuropathy were all caused by a common agent or mixture of agents, it is unlikely (although not impossible) that the illness observed was due to cyclopentane.

Since NIOSH, OSHA and ACGIH all concur with the OEL of 1270 mg/m^3 (Federal Register, 1989*b*), and since these occupational limits constitute the best available toxicity information currently available for cyclopentane, the OEL is used to drive the ITSL derivation. However, it should be noted that, given the sparse nature of the toxicology database for this chemical and the rather vague basis for the specific TLV concentration chosen, continuing efforts should be made to identify and utilize new health-based data to re-evaluate and update the ITSL, should such data become available.

ITSL Derivation: Per Rule 232(1)(c) of Act 348:

$$\textbf{ITSL} = \text{OEL} \times \frac{1}{100} = 1720\ \text{mg/m}^3 \times \frac{1}{100} = 17.2\ \text{mg/m}^3 \times \frac{1000\ \mu\text{g}}{1\ \text{mg}} = \textbf{17,200}\ \mu\text{g/m}^3$$

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 cyclopentane 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 factor 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.

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