MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

May 26, 1995

TO: File for Caprolactam (CAS # 105-60-2)

FROM: Dan O'Brien

SUBJECT: Initial threshold screening level (ITSL) for caprolactam

The initial threshold screening level for caprolactam is 10 $\mu g/m^3$ 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.

Caprolactam is used commercially primarily as a monomer for synthetic fibers, plastics, coatings, plasticizers and paint vehicles, and as a cross-linking agent for polyurethanes (ACGIH, 1991). It has also been used as a solvent for some high molecular weight polymers (Merck, 1983), in the synthesis of the amino acid lysine (Hawley, 1981), and as an insecticide (Sharma and Reddy, 1987). Physically, it is a highly water soluble, hygroscopic powder with a vapor pressure sufficient to allow it to also exist in the air as a vapor (IRIS, 1994).

Toxicological data on caprolactam are somewhat limited. Gross (1984) has reviewed the biological activity of the compound, and reports that the primary high-dose acute effects in animals are neurologic, respiratory and cardiovascular. The neurological effects are characterized by apprehension, tremors (Goldblatt et al., 1954) and tonic/clonic seizures, which are thought to be mediated by antagonism of the neurotransmitter γ-aminobutyric acid (GABA)(Gross, 1984). Caprolactam is a respiratory stimulant and can be hyper- or hypotensive, depending on dose. No-effect levels reported following acute to subchronic inhalation exposures in various rodent species range from 0.06-261 mg/m^3 (ACGIH, 1991; Gross, 1984). Effects exhibited in longer term oral studies are generally limited to mild but reversible growth and body weight depressions, and corresponding increases in liver and kidney weights (ACGIH, 1991; Gross, 1984; NTP, 1982). One three-generation developmental study in rats (Serota *et al.*, 1984) found these

body weight depressions to occur in animals exposed *in utero* and through early life as well.

U.S. EPA has concluded that the toxicological database for caprolactam is insufficient to derive an inhalation Reference Concentration (RfC), as no adequate long-term studies examining the effects of inhalation exposure exist (IRIS, 1994). The IRIS (1994) RfC documentation notes that the compound is "a respiratory tract irritant, and no data exist to definitively rule out portal-of-entry effects associated with long-term chronic inhalation exposure. No inhalation pharmacokinetic data exist for this compound". Rodent kinetic studies by Waddell *et al.* (1984) found rapid dissemination of both oral and intravenous doses of [^{14}C]caprolactam throughout the bodies of both male and female Swiss-Webster mice, as measured by whole-body autoradiography. The chemical passed the placental barrier to fetuses in five pregnant females dosed; concentration in the fetuses was greater than that in maternal tissues, but decreased with time. With the exception of the fetuses, and maternal liver and kidney, the only anatomical sites with residual radioactivity nine hours after exposure were nasal epithelium and the olfactory lobe of the brain. The authors attributed the nasal retention to one or more unnamed metabolites, and considered the olfactory lobe retention to be an artifact of the mode of death (freezing in dry ice/hexane). EPA has suggested that these limited available pharmacokinetic data "are not suitable for purposes of oral-to-inhalation extrapolation because they are not the appropriate route and provide no information on identity of circulation metabolites. The latter issue may be especially relevant because portal-of-entry tissues capable of metabolism (nasal epithelium) show retention of radiolabeled caprolactam". Given these points, the use of oral data to assess the human health risk of caprolactam inhalation is of questionable validity, and though an RfD is currently available for caprolactam (IRIS, 1994), it is not considered appropriate for use in the derivation of a screening level.

The International Agency for Research on Cancer (IARC, 1986) has reviewed the carcinogenicity and mutagenicity of caprolactam, and found no evidence of carcinogenicity in animals and no data on carcinogenicity in humans, which led them to categorize the chemical as Group 4, meaning that no evaluation of human carcinogenicity could be made. Among the data reviewed was a 2 year feed study in Fischer 344 rats and B6C3F$_1$ mice carried out by the National Toxicology Program (NTP), in which caprolactam was concluded to be negative for carcinogenicity in both sexes of both species under the conditions of the study (NTP, 1982). Furthermore, caprolactam's mutagenic potential appears extremely limited, with all of the tests carried out by NTP negative. Of the studies reviewed by IARC (1986), only 6 of 36 studies in mammalian cells obtained positive responses; of those six, three were cell transformations and three were chromosomal effects. Thus, the available data do not support the use of mutagenic and carcinogenic effects to drive the derivation of a screening level.

The data of the greatest potential use in formulating an ITSL derive from occupational exposures. Much of the occupational work has been carried out by German and Russian workers, and consequently the original studies were unavailable for review. However, the RfC data summary (IRIS, 1994), the TLV documentation (ACGIH, 1991), and Gross (1984) have all summarized parts of this body of data. Some of the effects reported in German workers after acute exposure to a reported concentration of 61 mg/m^3 are analogous to neurologic signs in animal studies, namely, irritability and nervousness (Hohensee, 1951). Other complaints included a bitter taste, nosebleeds, dry and irritated upper respiratory passages, and flatulence. Various Russian investigators describe diverse complaints and abnormalities in people exposed to caprolactam in nylon-producing factories. These are extensively discussed by Gross (1984). Effected organ systems included gastrointestinal (nausea, belching, heartburn, inappetance, chronic gastritis, gastric and duodenal ulcerations), cardiovascular (electrocardiographic abnormalities, pain and palpitations), reproductive (menstrual abnormalities, post-partum hemorrhage, pregnancy toxemia, premature delivery, uterine hypotonia during labor), and neurologic (neuroses, neurasthenia, polyneuritis and -radiculitis, hyper- and paresthesia, hyper- and hyporeflexia, irritability and rapid mood shifts, decreased corneal sensitivity). Dermatoses (primarily of the hands) were apparently prevalent as well, with half of the exposed workers effected; ten percent of those cases were "severe and persistent after prolonged contact". Two reports noted skin hypersensitivity (thought to be due to "an autoimmune component" in over half of the effected workers. With respect to the report of autoimmunity, Street (1981) elaborated that "Brusilovskii and coworkers (1973) detected autoantibodies in patients exposed to caprolactam" but that "autoimmune reactions are probably quite dose-dependent and, therefore, unlikely to become manifest as a low dosage phenomenon". While such a extensive collection of reported health effects is certainly a cause for concern, as Gross (1984) has noted, the effected workers were in no instance exposed solely to caprolactam; confounding chemical exposures included cyclohexane, -hexanol and -hexanone, benzene, acetone , trichloroethylene and biphenyl. High ambient temperature, humidity and noise levels may have contributed to or been responsible for a portion of these illnesses as well. Moreover, methodological inconsistencies (*e.g.*, over ten percent of the controls had similar health complaints as the exposed workers) and deficiencies in reporting, data presentation and exposure assessment leave the accuracy of these reports open to question. Nevertheless, as IRIS (1994) has noted, the fact that the health effects reported, especially the reproductive endpoints, are internally consistent among many occupational studies, and with some animal studies, points to an area of uncertainty that has not, as yet, been adequately assessed.

Limited studies by Ferguson and Wheeler (1973) report primarily irritative effects, both dermal and respiratory, especially in response to dust exposure. These authors also summarized the medical histories of an unknown number of employees exposed to caprolactam vapor. They noted 1) no differences in general health among the exposed as compared

to the non-exposed; 2) over eighteen years, three cases of skin irritation serious enough to require medical attention (following direct contact with the agent); 3) dose-related nose and throat irritation above 10 ppm (47 mg/m^3) which became "severe" and "incapacitating" at 100 ppm (470 mg/m^3); eye irritation accompanied these symptoms at concentrations in excess of 25 ppm (118 mg/m^3); 4) low humidity seemed to exacerbate the symptoms, and individuals differed markedly in susceptibility; and 5) no distress was noted at concentrations ranging up to 7 ppm (33 mg/m^3). These same authors carried out some experimental vapor exposures to a group of five volunteer workers (adult males not continuously exposed to caprolactam), who reported their subjective symptoms after a momentary exposure at various distances from a source. Measured exposures ranged from 10-104 ppm (47-489 mg/m^3). Again, effects were irritative, and more severe at higher concentrations; all subsided on cessation of exposure. Ferguson and Wheeler's study had a number of methodological deficiencies, mainly with respect to exposure assessment; these are discussed at length in the RfC data summary (IRIS, 1994).

The remaining occupational literature (including the references which appear to have primarily influenced the setting of the TLV and the National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Level (REL)) was not available for review. A small matched case-control study (Billmaier *et al.*, 1992) investigating the association between caprolactam exposure and lower respiratory disease (via spirometry) is discussed by IRIS (1994), but again, methodological problems (small sample size, poor quality assurance, no investigation of upper respiratory endpoints) limit its usefulness for use in derivation of a screening level. ACGIH (1991) cites unpublished reports of Brief (1972) and Ferguson (1972) as the basis for setting the TLV-Time Weighted Average (TWA) for caprolactam dust at 1 mg/m^3 "to reduce the potential for irritation of the skin, particularly when wearing respirators". ACGIH recommended a TLV-TWA of 23 mg/m^3 for caprolactam vapor, also to reduce the potential for irritation. Short Term Exposure Limits (STELs) of 3 mg/m^3 and 46 mg/m^3 for dust and vapor, respectively, have also been set. In 1988, ACGIH proposed to lower the TLV-TWA for caprolactam vapor to 1 mg/m^3, but this change was never adopted. The Occupational Safety and Health Administration (OSHA), in setting its Permissible Exposure Limits (PELs), has noted (Federal Register, 1989) that NIOSH did not concur with the TLV for caprolactam vapor; NIOSH has set the REL for both the dust and vapor phases at 1 mg/m^3, with short term limits of 3 mg/m^3 (NIOSH, 1994, 1992). The rationale for this decision (Federal Register, 1989) is also noted by OSHA: "...NIOSH observed that `the proposed PEL does not appear to provide a sufficient margin of safety to caprolactam vapor', based on available human exposure responses". A previous section of the same document cites the work of Hohensee (1951) as reporting "The health effects of exposure to caprolactam vapor are identical to those described for caprolactam dust, except that contact with the vapor is reported to be even more irritating", and one can only speculate that this is the basis for NIOSH's REL.

Given the previously noted fact that EPA (IRIS, 1994) has judged the available data inadequate to derive an RfC, and also insufficient to justify oral-to-inhalation extrapolation (such as would be required to utilize the RfD or long-term rodent studies), the occupational exposure limits (OEL) represent the best available data for use in derivation of an ITSL. And, as stipulated in rule 230(1)(c) of Act 451, the NIOSH REL of 1 mg/m3 for both dust and vapor forms of caprolactam is the most appropriate of the available OELs to drive the screening level, since this concentration is lower than the ACGIH TLV-TWA.

ITSL Derivation: Per Article II, Chapter 1, Part 55, Rule 230(1)(c) of Act 451:

$$\textbf{ITSL} = \text{OEL} \times \frac{1}{100} = 1\ \text{mg/m}^3 \times \frac{1}{100} = 0.01\ \text{mg/m}^3 \times \frac{1000\ \mu\text{g}}{1\ \text{mg}} = \mathbf{10\ \mu g/m^3}$$

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 caprolactam 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 a time-weighted average recommended exposure level, an **8 hour averaging** time applies.

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