MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for 1-ethyl-2-pyrrolidone (CAS # 2687-91-4)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: May 28, 2013

SUBJECT: Screening Level for 1-ethyl-2-pyrrolidone (CAS# 2687-91-4)

The initial threshold screening level (ITSL) for 1-ethyl-2-pyrrolidone (CAS # 2687-91-4) is 4.9 µg/m^3 based on an annual averaging time.

1-Ethyl-2-pyrrolidone (NEP; also known as n-ethyl-2-pyrrolidone and 2-pyrrolidinone) is a colorless to yellow liquid with a molecular weight of 113.16 g/mol. NEP is used: in adhesives and binding agents; in coloring agents; in corrosion inhibitors; in cosmetics; in softeners; as a stabilizer; in cleaning/washing agents; in pesticides and preservatives; in paints, lacquers, and varnishes; as laboratory chemicals; and as an intermediate in the manufacture of other chemicals (ACToR, 2012).

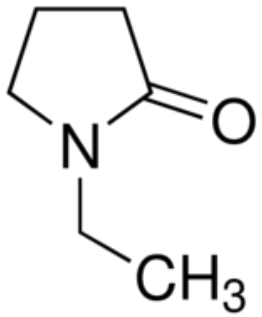

Figure 1. Structure of 1-ethyl-2-pyrrolidone.

A literature review was conducted to determine an initial threshold screening level (ITSL) for NEP. The following references and databases were searched to derive the above screening level: CCD, United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (TLV/BEI) 2012 guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), Acute Database, Chemical Abstract Service (CAS) Online (searched 3/13/13), National Library of Medicine

(NLM)-online, EPA Aggregated Computational Toxicology Resource (ACToR) Database, US EPA TSCATS database, and Hazardous Substances Data Bank (HSDB).

The best available basis for an ITSL derivation is a reproductive study by Saillenfait et al., (2007), in which pregnant Sprague-Dawley rats (9-12 rats/group) were orally administered NEP at doses of 0, 50, 250, 500, and 750 mg/kg/day by gavage on GD 6-20. "A significant increase in the percentage of post-implantation losses was observed at 500 and 750 mg kg^{-1} day^{-1} (7.0%, 25.2% and 95.8% at 0, 500 and 750 mg kg^{-1} day^{-1}, respectively)" (Saillenfait et. al., 2007). This effect was not increased at 50 and 250 mg/kg/day. Maternal weight gain was markedly depressed at all doses during the first three days of treatment. The reduction in weight continued, but was mainly attributed to the decreased fetal weight and/or to increased post-implantation loss. "At 750 mg kg^{-1} day^{-1}, there was a significant increase in the number of litters with dead fetuses. A severe reduction in the number of live fetuses was also observed, correlated with the high incidence of resorptions (i.e., 83%)….A distinctive dose-response pattern for external, visceral and skeletal malformations was seen, although no individual malformation was significantly different from control….At 750 mg kg^{-1} day^{-1} 26% of the fetuses exhibited edema….An increased incidence of supernumerary 14^{th} ribs was observed at 250 mg kg^{-1} day^{-1} and higher doses" (Saillenfait et. al., 2007). The no-observed-adverse-effect level (NOAEL) for developmental toxicity was considered to be 50 mg kg^{-1} day^{-1}. Maternal toxicity, as evidenced by decreased body weight gain and food consumption was observed at all doses at the beginning of treatment. The difference in body weight change from gestation day 0 to 21 was: 170 grams for controls; 154 grams for 50 mg/kg/day dose group; 142 grams for 250 mg/kg/day; 128 grams for 500 mg/kg/day dose group; and 74 grams for the 750 mg/kg/day dose group. The greatest difference was found in gravid uterine weight: control female gravid uterine weight was 104 grams; 94 grams for females at 50 mg/kg/day dose; 90 grams for the 250 mg/kg/day dose; 72 grams at 500 mg/kg/dose; and 16 grams for females at the 750 mg/kg/day dose. After evaluating the data by benchmark dose software, the significant difference from the control group to the dose groups, the P value is <0.01 using the polynomial model with 0.95 confidence level. Due to the decrease in maternal weight gain and gravid uterine weight it is prudent to use the uncertainty factor of 3 for LOAEL to NOAEL in the equation below. The lowest-observed-adverse-effect level (LOAEL) for maternal toxicity was considered to be 50 mg/kg/day. "Adverse effects on development, which included severe malformations, were seen at doses which also caused maternal toxicity" (Saillenfait et. al., 2007).

According to Rule 232(1)(e), an ITSL can be derived from a 7-day oral study using the following equation:

$$ITSL = \frac{LOAEL}{35 \times 100 \times UF} \times \frac{W_A}{I_A} \times \frac{b}{a}$$

Where, UF is the uncertainty factor which will be 3 for the use of a LOAEL. W_A is the weight of a female Sprague-Dawley rat in kg (0.338 kg), I_A is the daily inhalation rate of female Sprague-Dawley rats in cubic meters/day, *b* is the absorption efficiency by the

oral route of exposure and *a* is the absorption efficiency by the inhalation route of exposure. Since, the absorption efficiencies of 1-ethyl-2-pyrrolidone are not known the values for *b* and *a* are 1. Before determining the ITSL, the value of I_A must be ascertained using the following equation taken from EPA (1988):

$$I_A = 0.80 \times W^{0.8206}$$

Where I is inhalation rates in m^3/day and W is the body weight of a female Sprague-Dawley rat in kg (0.338 kg). Entering this data into the equation for I_A gives:

$$I_A = 0.80 \times 0.338^{0.8206} = 0.328487639\ {}^{m^3}/_{day}$$

Using the daily inhalation rate calculated above, with the LOAEL of 50 mg/kg/day for maternal toxicity and putting this information into the equation for determining the ITSL above:

$$ITSL = \frac{50\ {}^{mg}/_{kg/day}}{35 \times 100 \times 3} \times \frac{0.338\ kg}{0.328487639\ {}^{m^3}/_{day}} \times \frac{1}{1} = 0.0048998\ {}^{mg}/_{m^3} = 4.9\ {}^{\mu g}/_{m^3}$$

According to Rule 232(2)(c) the averaging time is annual. The initial threshold screening level (ITSL) for 1-ethyl-2-pyrrolidone (CAS # 2687-91-4) is 4.9 µg/m^3 based on an annual averaging time.

References:

ACToR. 2012. Chemical Summary: 1-ethylpyrrolidin-2-one (2687-91-4). ACToR: Aggregated Computational Toxicology Resource. Available online at: http://actor.epa.gov/actor/GenericChemicalPdfServlet?casrn=2687-91-4

APCR. 2013. Air Pollution Control Rules, Promulgated pursuant to Part 55, Air Pollution Control, of the Natural Resources and Environmental Protection Act, Michigan Department of Environmental Quality. 1994, Act 451, as amended (NREPA).

EPA. 1988. Recommendation for and documentation of biological values for use in risk assessment. PB 88-179874.

Saillenfait, AM; Gallissot, F; and Sabaté, JP. 2007. Developmental toxic effects of *N*-ethyl-2-pyrrolidone administered orally to rats. Journal of Applied Toxicology. 27:491-497.

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