MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: Nonylphenol file (CAS # 25154-52-3)

FROM: Gary Butterfield

SUBJECT: Screening level for Nonylphenol

DATE: July 6, 2006

Nonylphenol (NP) under this CAS number can be described as being composed of mixed isomers of nonylphenol. Possible isomers include 2-nonylphenol (CAS # 136-83-4), 3-nonylphenol (CAS # 139-84-4), and 4-nonylphenol (CAS # 104-40-5). The para- substituted isomer occurs predominately. In addition, 4-nonyl-branched phenol (CAS # 84852-15-3) is some times used synonymously under CAS # 25154-52-3. Generally, commercial nonylphenol is most often assigned to CAS # 84852-15-3.

Nonylphenol is a pale yellow liquid at ambient temperatures. This material has a molecular weight of 220.4 g/mol. The melting point is 2C. The boiling point is 293C. The vapor pressure for this material quite low, reported to be at $3x10^{-5}$ mmHg. The water solubility is pH dependent with greater solubility with higher pH. The water solubility of 6 mg/L is reported at a pH of 7. Nonylphenol is a known endocrine disruptor, that is not too potent when compared to estrogen or DES. It most frequently comes to exist in the environment from the breakdown of nonylphenol ethoxylate surfactants. These surfactants are used as oil soluble detergents and emulsifiers. Large amounts of nonylphenol are produced in the US, approximately 230 million pounds was reportedly produced in 1998.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH) Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), Michigan Department of Environmental Quality (DEQ) library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1968 – March 2005), National Library of Medicine (NLM) - Toxline, and National Toxicology Program (NTP) Status Report.

The CAS and NLM on-line literature searches were conducted on April 4, 2005. There are numerous studies evaluating the endocrine disruption and reproductive effects of exposure to NP. The route of exposure from most of these studies is oral – either in the diet, drinking water or by gavage.

An example of a non-reproductive study was conducted by Cunny et al (1997). In this 90-day rat study, diets of 0, 200, 650 or 2000 ppm (converted to 0, 15, 50 or 150 mg/kg by authors) were fed to groups of 15 Sprague-Dawley rats of each sex. This study used nonylphenol with CAS # 84852-15-3 that was 95.6 % pure. The control and high dose groups also had an extra 10 of each sex additional rats, which were held for a 4-week recovery period at the end of the

90 days of dosing. The NOAEL in this study was reported by the authors to be 650 ppm or 50 mg/kg. The adverse effects observed in the highest dose, 2000 ppm or 150 mg/kg, included a slight decrease in body weight, and increased male kidney organ weight, and a decrease in renal hyaline droplets. These effects disappeared following the 4-week recovery period.

The NOAEL in many of the multi-generation reproductive studies is lower (approximately 10 mg/kg) than that the 90-day feeding study by Cunny et al. The two generation Sprague-Dawley rat gavage study by Nagao et al (2001) is a good example of these multi-generation studies. The nonylphenol in this study used CAS # 25154-52-3 that was 99.0 % pure. Groups of 25 rats of each sex were gavaged daily. The doses that were administered were 0, 2, 10 or 50 mg/kg. The adverse effects that were observed to be occurring at 50 mg/kg in first and second generations include: altered liver and kidney organ weight and histopathology, reduced pup viability, and altered hormone levels. The NOAEL for this study is 10 mg/kg.

In the NTP 3 generation study reported by Chapin et al (1999), groups of Sprague-Dawley rats were fed diets containing 0, 200, 650 or 2000 ppm (converted to 0, 9 to 35, 30 to 100, or 100 to 350 mg/kg – where the ranges are dependant on various pup sizes and food consumption rates). This study reported that the nonylphenol was the branched nonylphenol with CAS #84852-15-3. Due to the synonymous use of nonylphenol and branched nonylphenol, and the likely little toxic difference between them, the use of the 84852-15-3 data for 25154-52-3 screening level development is considered to be appropriate. The high and mid doses of this study had reduced body weight gain, and reproductive effects consisting of decreased time to vagina opening, and decreased uterine weight. All dose groups were found to have male kidney increased organ weight, with tubular dilation and cyst formation. Therefore, the low dose of 9 mg/kg in this study is considered to be a LOAEL.

Given the fact that there is a general lack of any inhalation toxicity information for this chemical, the screening level will be calculated from the oral information. It is being assumed that there will be no route of exposure critical toxic effect that will occur from exposure to this chemical . Therefore, the inhalation screening level can be calculated from the above oral studies using EPA's RfD methodology, and then determining the ITSL under R232(1)(b), as follows.

RfD = (9 mg/kg)/(10x10x10) = 9 ug/kg
An uncertainty factor of 10 for each of intra-species sensitivity, inter-species, and LOAEL-to-NOAEL was used in the above RfD calculation.

ITSL = 9 ug/kg x (70 kg)/(20 m3) = 32 ug/m^3
The ITSL is being rounded to 30 ug/m^3 with a 24 hour averaging time.

References:

Chapin et al. 1999. The effects of 4-nonylphenol in rats: a multigeneration reproduction study. Toxicol Sci 52: 80-91.

Cunny et al. 1997. Subchronic toxicity (90-day) study with para-nonylphenol. Reg Toxicol Pharm 26: 172-178

Nagao et al. 2001. Reproductive effects of nonylphenol in rats after gavage administration: a two generation study. Repro Toxicol 15: 293-315.