MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: Dextromethorphan hydrochloride file (CAS # 6700-34-1)

FROM: Gary Butterfield

SUBJECT: Screening level for Dextromethorphan hydrochloride

DATE: May 22, 2007

Dextromethorphan hydrochloride (CAS # 6700-34-1) is a common ingredient in cold medicines. Other names are dextromethorphan hydrobromide (CAS # 125-69-9) or just dextromethorphan (CAS # 125-71-3). This material is a white crystalline solid. The molecular weight is 271.4 g/mol. The molecular formula is $C_{18}H_{25}NO$. The melting point of is 123C.

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 - April 2007), 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 23, 2007.

There is surprisingly little toxicity data for this commonly-used cough medicine. In most of the longer term or multiple dose toxicity data, dextromethorphan was only one component of a complex medicine mixture that was administered. Therefore, it is difficult to attribute any adverse effects observed to only one of the components of a complex mixture.

In the Borodkin and Sundberg (1971) article, the LD50 in female Swiss-Webster mice was reported to be 210 mg/kg. Groups of 10 young female mice , weighing approximately 16 to 24 g, was administered via gavage after being dissolved in methylcellulose. The LD50 was calculated by the Litchfield and Wilcoxon method.

The acute mouse oral LD50 of 210 mg/kg was used to determine the ITSL using R232(1)(h) as follows.

$$\text{ITSL} = \frac{210\ \text{mg/kg}}{500\text{x}40\text{x}100\text{x}0.167} \times \frac{1\ \text{kg}}{1.7\ \text{m3}} = 0.4\ \text{ug/m3 annual average}$$

In an abstract of a Sprague-Dawley rat 30-day oral study (Shuey et al (2004)), groups of rats were administered dextromethorphan at doses of 120 mg/kg to females, and 150, 275 or 400 mg/kg to males. An evaluation of possible brain neuronal changes by this NMDA receptor antagonist were conducted. Although this abstract mentions deaths occurring at the highest doses, no incidences of this occurrence was given in the abstract. It was reported that there were no brain histologic changes consistent with other NMDA antagonist observed in the dextromethorphan rats. Details from this abstract are considered to be insufficient to be able to establish a finalized screening level, but could be used here as the basis for a quick comparison to the PAI.

An evaluation of possible screening level development using this 30-day repeated dose study lowest dose level assumed to be the NOAEL, can follow R232(1)(e) as follows.

$$\text{ITSL} = \frac{125\ \text{mg/kg}}{35\text{x}100} \times \frac{1\ \text{kg}}{0.9\ \text{m}^3} = 47\ \text{ug/m}^3\ \text{annual average}$$

Both of the above possible ITSL calculations indicate that there potentially could be a wide range for the possible screening levels depending on what toxicity data is available. Due to the currently limited available toxicity data, it is considered best to utilize the lower of the two possible ITSL's calculated above, 0.4 ug/m^3 with annual averaging, when setting the ITSL for dextromethorphan, until more substantial toxicity data can be obtained.

References:

Borodkin and Sundberg. 1971. Polycarboxylic acid ion-exchange resin adsorbates for taste coverage in chewable tablets. J Pharmaceutical Sciences 60: 1523-7.

Shuey et al. 2004. Dextromethorphan does not cause neuronal vacuolation or degeneration in the posterior cingulated/retrosplenial cortex of rats. Toxicologist 78 page 62, abstract # 301.