MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

January 13, 2004

TO: File for ethyl lactate (97-64-3)

FROM: Marco Bianchi

SUBJECT: Initial Threshold Screening Level

The Initial Threshold Screening Level (ITSL) for ethyl lactate is 20 $\mu g/m^3$ based on an annual averaging time. The following references or databases were searched to identify data to determine the ITSL/IRSL: IRIS-online, HEAST, NTP Management Status Report-online, RTECS, EPB-CCD, EPB library, CAS-online, NLM-online, IARC-online, NIOSH Pocket Guide, and ACGIH Guide.

A complete reference check was conducted on ethyl lactate, but information was limited to an acute and subacute toxicological review. The data obtained from this review are from an extensive testing program on L-lactate esters carried out in the Netherlands. The types of toxicological testing included: acute oral, acute inhalation, skin and eye irritation, mutagenicity, developmental, and repeat inhalation tests. In addition, metabolic products are briefly reviewed to give some indication of potential for systemic toxicity of specific lactate esters. Although this review evaluated a number of lactate esters, this chemical evaluation will be limited to ethyl lactate.

Acute oral and inhalation studies were conducted according to good laboratory practices and OECD Guidelines 401 and 403, respectively. For the acute oral toxicity testing, no mortality was seen in rats for racemic ethyl lactate at 5000 mg/kg/body wt., and 2500 mg/kg/body wt. in mice. In the acute vapor inhalation study, 5 rats/sex/group were exposed nose-only for 4 hours at a target concentration of 5000 mg/m^3, the highest vapor concentration obtained using a compressed air nebulizer. Clinical observations, mortality, body weights, and gross pathological changes were recorded during a 14-day observation period. No mortality was noted, but clinical signs included decrease in breathing rate, piloerection, wet nares, and lachrymation. Gross necropsy revealed pale lungs with spots. Rats treated with racemic ethyl lactate in an acute dermal study resulted in a LD_{50} of greater than 5 g/kg body wt.

Twenty-eight-day inhalation studies in rats conducted on four L-lactate esters identified the nasal epithelium as the target organ. It is thought that the nasal effect seen in the inhalation studies is due to lactic acid, a hydrolysis product of lactate esters. Inhalation of alcohols has not been reported to cause this type of effect. The *in vitro* hydrolysis of various lactate esters in the rat nasal epithelium demonstrated a rapid enzymatic hydrolysis. In addition to the hydrolysis in the nasal cavity, the *in vitro* and *in vivo* hydrolysis of ethyl-L-lactate in the gastrointestinal tract of rats was evaluated. Ethyl-L-lactate was detected in the portal blood following intragastric instillation, supporting partial absorption of ethyl-L-lactate before hydrolysis. In an *in vitro* experiment, rat plasma hydrolyzed 80% of ethyl-L-lactate in 60 min at room temperature. In summary, for all lactate esters tested; the clinical signs, the lack of mortality, and the target organ effects are the same. The acidity of lactic acid is the common factor in all cases and most likely responsible for any clinical effects noted in the reported oral and inhalation studies.

Other short-term toxicity testing showed ethyl-L-lactate to be relatively low in toxicity. Mutagencity testing using Ames test strains TA98, 100, 1535, 1537, and 1538 with and without metabolic activation resulted in no microbial activity. In a dermal developmental study, ethyl-L-lactate was applied percutaneously on the back at 0, 517, 1551, or 3619 mg/kg to groups of 25 pregnant rats on days 6-15 of gestation. No deaths occurred in this study. Slight erythema and desquamation was seen in the treated animals. No other clinical signs or necropsy observations were noted. No effects were noted on developmental indices, gross external, soft tissue, or skeletal examination. The top dose tested was considered a NOAEL for developmental effects.

Two 28-day rat inhalation studies were conducted using OECD Guideline 412. Both subacute studies used 5 rats/sex/group (strain not mentioned), and exposed them 6 hrs/day, 5 days/wk to either 0, 150, 600, or 2500 mg/m^3 or to 0, 25, 75, or 200 mg/m^3. No treatment-related clinical signs, changes in body weight, food intake, hematology, biochemistry, or organ weights were noted following ethyl-L-lactate exposure up to 600 mg/m^3. At the top dose (2500 mg/m^3) body weight gain (decreased), food consumption (decreased), blood glucose (increased, males), urea levels (lower), absolute liver weight (decreased), adrenal and testes weights (increased) were statistically significantly different from the control. The NOAEL for systemic toxicity was 600 mg/m^3. Degenerative changes of the nasal olfactory epithelium and hyperplasia of the nasal respiratory epithelium, including hyperplasia of the goblet cells were noted at 600 mg/m^3 and higher. The NOAEL for local toxicity was 200 mg/m^3.

Therefore, the NOAEL for this study is 200 mg/m^3.

The ITSL was derived as follows:

NOAEL = 200 mg/m^3
25 = uncertainty factor; to account for using a NOAEL for a 28-day exposure period to estimate a NOAEL for a lifetime study.
100 = uncertainty factor; to account for specie differences and human population sensitivities.

$$\text{ITSL} = \frac{\text{NOAEL}}{35 \times 100} \times \frac{\text{hours exposed/day}}{24 \text{ hrs/day}}$$

$$\text{ITSL} = \frac{200 \text{ mg/m}^3}{25 \times 100} \times \frac{6 \text{ hrs/day}}{24 \text{ hrs/day}} = 0.020 \text{ mg/m}^3$$

Conversion of mg/m^3 to ug/m^3

$$\text{ITSL} = 0.020 \text{ mg/m}^3 \times \frac{1000 \text{ ug}}{1 \text{ mg}} = 20 \text{ ug/m}^3$$

The ITSL for ethyl lactate = 20 μg/m^3 based an annual averaging.

Reference:

1. Clary, JJ. et al. 1998. Safety assessment of lactate esters. Regulatory Toxicology and Pharmacology 27; 88-97.