MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

April 6, 2016

TO: File for Ethyl-3-Ethoxypropionate (CAS No. 763-69-9)

FROM: Mike Depa, Air Quality Division, Toxics Unit

SUBJECT: ITSL Derivation

Previously, the averaging time (AT) assigned to was 24 hours, as per the default methodology (Rule 232(2)(b))(see attached document: Recommendations Of The Scientific Advisory Panel dated 12/8/1994). The current file review concludes that the AT may appropriately be set at annual, based on the nature and duration of the key study and the initial threshold screening level (ITSL) value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is set to annual.

The ITSL for ethyl-3-ethoxypropionate is 134 µg/m^3 based on an annual averaging time.

RECOMMENDATIONS OF THE SCIENTIFIC ADVISORY PANEL
ETHYL-3-ETHYOXYPROPIONATE

CAS # 763-69-9
DECEMBER 8, 1994

Basis for ITSL: An Acceptable Ambient Concentration (AAC) was derived for ethyl-3-ethoxypropionate in 1991. The term AAC was used prior to the promulgation of the Air Toxics Rules. The AAC was derived and used in a similar manner as the current screening levels although some differences exist between the two methodologies.

The AAC for ethyl-3-ethoxypropionate was established at 3 µg/m³ based on annual averaging time. This value was based on an LC50 from Eastman Kodak. At the time of derivation, only summary information on studies from Eastman Kodak were available on an MSDS. This data was supplemented via conversations with Kodak staff, providing details on the acute toxicity studies. Although the MSDS mentioned a 90 day study and a teratology study, details were not available for AQD review.

Summary of Public Comment:
The American Automobile Manufacturer's Association provided public comments on this chemical. They noted the longer term studies mentioned on the Eastman Chemical MSDS and requested the review of these studies.

Response to Public Comment:
In response to the public comments, internal studies were pursued, obtained and reviewed. Although data was no longer available from Eastman Kodak, study details were available from Eastman Chemical Company. The new data provides better information on which to base a screening level. Eastman Chemical provided a number of internally generated studies, including: An Ames assay for mutagenicity; a four week oral toxicity study using rats; a 90-day inhalation toxicity study in rats; inhalation developmental toxicity studies in rabbits and in rats. Doses in the developmental toxicity studies were 125, 250, 500, and 1000 ppm. Doses in the 90 day rat inhalation study included 250, 500 and 1000 ppm.

In both inhalation developmental toxicity studies and in the 90 day rat inhalation study, a LOAEL of 250 ppm could be discerned. At this dose level in the developmental toxicity studies, slight maternal toxicity was observed as evidenced by significant decreases in feed intake (rats and rabbits) and mean body weight gain (rats). Decreased body weight gain was also seen in the 250 ppm male and female rats in the 90 day study. Although the change was not statistically significant at 250 ppm in males in the 90 day assay, there was a dose related trend with significant decreases in body weight at all higher dose levels. Terminal body weights were significantly reduced at all dose groups in females in the 90 day study. Also, there was a statistically significant increase in relative kidney weights in males and females in all dose groups in the 90 day study.

Adverse effects at higher doses included:
1) From the developmental toxicity study in rats: In addition to decreased mean body weight of dams at 500 and 1000 ppm, clinical signs of lethargy, salivation and reddish discoloration of jaw hair in females exposed to 1000 ppm; slight increases in the incidence of “minor internal soft tissue alterations and skeletal variants” were noted in litters at 1000 ppm; appearance of rudimentary thoracolumbar ribs was increased in litters at the high dose group. Authors concluded that 250 ppm and above doses were slightly maternally toxic and that 1000 ppm was slightly fetotoxic.

2) From the developmental toxicity study in rabbits: In addition to the decreased mean food consumption, some females had lacrimation at the 500 and 1000 ppm levels. These effects improved during treatment in all groups. Observations of reduced activity and closing of the eyes were noted and related to concentration. Labored breathing and salivation were increased in the 500 and 1000 ppm groups. The incidence of fetuses with major skeletal malformations at the 500 and 1000 ppm exposure levels was slightly higher than controls, however lack of consistency in type or severity of the malformations failed to indicate that they were treatment related. Authors concluded that 250 ppm and above groups exhibited slight maternal toxicity in the form of slightly reduced feed consumption. A NOAEL for developmental effects was concluded to be 1000 ppm.

3) From the 90 day inhalation study in rats: In addition to the body and kidney weight changes noted above, which impacted all dose groups, lethargy was noted at 1000 ppm; sialorrhea and lacrimation at 500 and 1000 ppm, discoloration of hair was seen at all dose groups and some alopecia was noted at 250 and 500 ppm. A slight concentration dependent increase in lymphocytes was seen in females, statistically significant in the high dose group. AST was significantly reduced in females at all dose groups (high control values may be responsible for the difference). Relative liver weights were significantly increased in the 1000 ppm males and in 500 and 1000 ppm females. Relative testes weights showed a concentration dependent increase, significant only at the 1000 ppm level. Absolute heart weights were decreased in an exposure-dependent fashion, significantly at 500 and 1000 ppm males. Relative brain weights were statistically elevated in the 500 and 1000 ppm females. Because of the “non-specific nature” and lack of target tissue, the authors concluded that 250 ppm was a NOAEL.

The 125 ppm level was clearly a NOAEL in the developmental toxicity studies. The authors of the 90 day study felt that 250 ppm could be considered a NOAEL. However, since significant body weight changes were noted and a variety of organ weight trends were seen in the 90 day study; there were irritant properties noted at 250 ppm; and 250 ppm was slightly maternally toxic in the developmental studies, a 250 ppm dose will be considered an LOAEL for derivation of an inhalation reference concentration and for use in screening level derivation. Since an adequate 90 day study is available, an inhalation RfC will be derived using guidelines from U.S. EPA “Interim Methods for Development of Inhalation Reference Concentrations”, August 1990 (Equations taken from this

document are specified in parentheses below). This RfC will be used for calculating an Initial Threshold Screening Level (ITSL):

Actual concentrations in the 90 day study were 251, 510, 996 ppm
EEP molecular weight = 146.2

ppm - mg/m³ conversion: 251 ppm x 146.2/24.45 = 1500.87 or 1501 mg/m³ (Eq.4-2(b))

$LOAEL_{ADJ}$ = 1501 mg/m³ x 6hr/24hr x 5days/days7 = 268 mg/m³ (Eq.4-3)

$LOAEL_{HEC}$ = 268 mg/m³ x $lambda_a/lambda_h$ = 268 mg/m³ x 1 = 268 mg/m³ (Eq.4-10)

Since the blood to air partition coefficient in the above equation is unknown for this compound, the ratio of $lambda_a/lambda_h$, is assumed to be 1.

RfC = $LOAEL_{HEC}$/UF = 268mg/m³ /(10x10x10x2) = 0.134 mg/m³ = 134 µg/m³ (Eq.4-1)

The uncertainty factors include 10 for interspecies, 10 for intraspecies variation, 10 for duration of study less than chronic and 2 for use of a LOAEL. The uncertainty factor for use of a LOAEL was reduced from 10 to 2 based on the mild nature of the effects seen.

ITSL = RfC = 134 µg/m³ based on 24 hour averaging

Panel Recommendations:
The Panel recommends a screening level or 134 based on 24 hour averaging.

References:
1. Katz, G., 1986, “90-Day Inhalation Toxicity Study of Ethyl 3-Ethoxypropionate in the Rat”, Eastman Kodak Company, (Obtained from Eastman Chemical Co., Kingoport, TN).

2. Bio/dynamics Inc., 1987, “An Inhalation Developmental Toxicity Study in Rabbits with Ethyl 3-Ethoxypropionate”, Eastman Kodak Co., (Obtained from Eastman Chemical co., Kingsport, TN).

3. Krasavage, W. and Katz, G., 1984, “The Developmental Toxicity of Ethyl-3-Ethoxypropionate in the Rat”, Eastman Kodak Co., (Obtained from Eastman Chemical co., Kingsport, TN).