MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

April 5, 2016

TO: File for 4-Ethyl Toluene (CAS No. 622-96-8)

FROM: Mike Depa, Air Quality Division, Toxics Unit

SUBJECT: ITSL Derivation

Previously, the averaging time (AT) assigned to 4-Ethyl Toluene was 24 hours, as per the default methodology (Rule 232(2)(b))(see attached memo from Michael Depa dated September 2, 2011). 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 ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is set to annual.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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September 2, 2011

TO: File for 4-Ethyl Toluene (CAS No. 622-96-8)

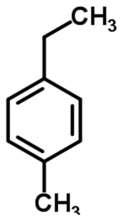
FROM: Michael Depa, Toxics Unit, Air Quality Division

SUBJECT: Screening Level Determination

The initial threshold screening level (ITSL) for 4-ethyl toluene (also known as p-ethyl toluene or PET) is 350 .µg/m³ (24-hr averaging time).

The following references or databases were searched to identify data to determine the screening level: Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1967- July 2011), National Library of Medicine (NLM), Health Effects Assessment Summary Tables (HEAST), and National Toxicology Program (NTP) Status Report. The EPA has not established a reference concentration (RfC) or reference dose (RfD) for PET. There are no occupational exposure limits for PET. PET is expected to be a liquid at standard temperature and pressure. The boiling point is 162°C and the vapor pressure is 3 mmHg @25°C. The molecular weight for PET is 120.19 g, and the molecular formula is C9H12. The molecular structure is shown in Figure 1.

Figure 1. Molecular Structure of 4-Ethyl Toluene (PET)



Animal Studies
In a well performed acute study, the rat oral LD5O for PET was reported as 4,850 mg/kg (95% confidence limits of 3,880 to 6,062) (Snell, 1978).

In an two-week oral study, groups of 5 male and 5 female F344 rats were dosed with 25, 50, 100, 200, 400, or 800 mg/kgl/day of PET in olive oil vehicle (Hazleton Labs,

1983). The control group consisted of 10 mate and 10 female rats and received the olive oil vehicle only. Criteria evaluated included mortality, appearance and behavior, body weights and food consumption, clinical laboratory data, organ weights and organ/body weight ratios, and gross pathology. Statistical comparison of mean body weights of the treated groups with the control group for each sex revealed a significantly lower mean terminal body weight for the 800 mg/kg males and females of the same dose at week 1 ($p<0.05$). Mean body weights for all other treated groups were comparable to the respective control group. Total food consumption for the 800 mg/kg females was significantly less than the control group ($p<0.05$), but all other treated groups were comparable to the control group of the same sex. The mean serum glutamic pyruvic transaminase (SGPT) value for the 800 mg/kg male rats was statistically higher than controls ($p<0.05$). Mean relative liver weights were significantly higher than control values for the 400 and 800 mg/kg males and females, and absolute liver weights were significantly higher than control for the 800 mg/kg males and the 400 mg/kg females ($p'<0.05$). Mean relative kidney weight for the males increased with increasing dose level with the 800 mg/kg dose group being significantly elevated ($p<0.05$). Given that the SGPT value elevated in the 800 mg/kg male dose group as well as having increase absolute and relative liver weights compared to control, this dose is clearly an adverse effect level. However, SGPT was not elevated in the 400 mg/kg level. It could not be determined whether the increased liver weight at the 400 mg/kg dose level was due to tissue damage or an increase in metabolic activity because a histopathology evaluation was not performed in this study.

In a teratology study, groups of 16 pregnant Dutch Belted rabbits were dosed by gavage with 0, 25, 125, 200 or 250 mg/kg/day of PET on gestation days 6 through 27 (IRDC, 1981). The reported results are shown in Table 1.

Table 1. Teratology Study Results (IRDC, 1981)

Dose (mg/kg)	Mortality (n=16)	Number of Rabbits Aborting	Increase in the number of fetuses (or litters) with malformations compared to control?
0	2	1	
25	1	1	No
125	3	4	No
200	0	2	Yes; Increase in skeletal variation of 13th rudimentary rib
250	12	2	Not given*

* severely reduced sample size as a result of high mortality

The number of rabbits aborting during the study at the 125 mg/kg dose level was 4 out of 16. The Fisher's exact P-test was performed at the 125 mg/kg dose level; P = 0.144. The no-observed-adverse-effect-level (NOAEL) for this study was determined to be 125 mg/kg.

In a pilot teratology study, groups of 5 pregnant CD rats were dosed by gavage with 0, 100, 300, 750, 1,500, or 3,000 mg/kg/day on days 6 through 19 of gestation (IRDC, 1980). PET was administered undiluted and control rats received distilled water. All rats

in the 3,000, 4 at 1,500 and I at 750 mg/kg/day died prior to Cesarean section. Decreases in mean maternal body weight gain were observed in all surviving dose groups. An increase in mean number of late resorptions was observed at the 100 mg/kg/day level, however, the authors conclude this was not treatment related as no dose-related trend was observed. Increases in early resorptions at 100, 300, 750 and 1,500 mg/kg/day with corresponding increase in mean post-implantation loss were also observed (statistical analysis of the data was not provided).

In a follow-up to the IRDC (1980) teratology study, IRDC (1981) performed another teratology study. Groups of 25 pregnant CD rats were dosed by gavage with 0, 25, 100 or 200 mg/kg on days 6 through 19 of gestation. Cesarean sections were performed on all females on gestation day 20. Survival was 100% in all dosage groups. There were no biologically meaningful differences in appearance, behavior or mean maternal body weight gain of rats in any of the treated groups were compared to the control group. There were no biologically meaningful or statistically significant differences in the mean numbers of corpora lutea, total implantation, early resorptions, postimplantation loss, viable fetuses, the fetal sex distribution, mean fetal body weight or the number of litters with malformation in any of the PET-treated groups when compared to the control group. The number of litter (and fetuses) with genetic and developmental variations in the PET-treated groups was also comparable to the control group. The authors stated that the treatment with PET did not produce a teratogenic response when administered orally, in corn oil vehicle, to pregnant rats at a dosage level of 200 mg/kg/day or less. The authors mentioned that in the pilot study (IRDC, 1980) rats given doses of loo mg/kg/day had an increased number of resorptions and post-implantation loss. The authors attributed the difference in the two studies to the use of undiluted PET in the pilot study, whereas the IRDC (1981) study used corn oil vehicle.

Groups of 20 male and 20 female F344 rats received gavage doses of 0, 100, 300 or 900 mg/kg PET for 13 weeks (Bornston Labs, 1983). Dose-related mortality was observed in the 300 and 900 mg/kg dose males and females. Significant body weight depression and lowered body weight gains were noted for the 300 and 900 mg/kg males throughout the course of the study. Body weights for the mid- and high-dose females were significantly lower than controls during the first four weeks of the study. The authors stated that there were no noteworthy differences in food consumption between control and treated groups. The authors stated that hematology data indicated hematoconcentration in male mid- and high-dose groups during week 5 which abated completely by week 13. No similar findings were observed in female treated groups. A leukocyte differential shift was evident in all treated male and female groups during weeks 5, 13 and 14 and consisted of increased numbers of segmented neutrophils with corresponding decreases in lymphocyte numbers in the treated male groups and increased numbers of both segmented neutrophils and lymphocytes ¡n the treated female groups. However, the increase in segmented neutrophils was significantly elevated only in the mid- and high-dose groups. The authors stated that the shift appeared to be treatment related in the mid- and high-dose males and high-dose females. Significant reductions in platelet cell number were observed in mid- and high-dose male and low- and mid-dose female groups by week 13, but not high-dose female rats. Treatment-related elevation in SGPT, ALP and albumin levels were present in the male and female mid- and high-dose groups during week 5, as well as significant

reductions in total cholesterol levels (mid- and high-dose males and high-dose females) and glucose levels (high dose males). Total protein levels for the high-dose males and females also were elevated at week 5. Treatment related elevations of SGPT, ALP. total protein, and albumin levels were confined to the high-dose males and females during week 13, as well as treatment related reductions in total cholesterol and glucose levels in the mid- and high-dose males. The authors stated that the results of urinanalysis were unremarkable. No treatment-related trends in gross necropsy data were evident. The absolute and relative liver weight of the 100, 300 and 900 mg/kg female groups were statistically increased compared to control rats ($p<0.05$) and a dose- related pattern was observed. Male rats had statistically significant increases ($p<0.05$) in relative liver weights at the low-, mid- and high-dose levels. The absolute liver weight in the male rat high-dose group was significantly higher but the low- and mid-dose groups were not. The authors stated that no corresponding liver lesions were seen upon histopathologic evaluation. The authors stated that, “Relative liver weights for the low-dose males and females were 3.9% and 6.4% higher than their respective control group. These slight increases were considered incidental to treatment.” Dose-related reductions in absolute and relative testes/epididymides weights of the mid-and high-dose males were observed. Microscopically, administration of PET was associated with testicular atrophy and hypospermatogenesis of the testes and hypospermia or aspermia of the epididymides in the high-dose males; a number of these animals had sperm granulomas in the epididymides. No microscopic indication of atrophy was seen in the sections of testicles from the mid-dose rats; however, two of the animals showed minimal hypospermatogenesis. Testicle sections from all low-dose male rats appeared normal. The authors stated that based on the results of this study, the no effect level for PET is 100 mg/kg/day. This conclusion is supported by the negative liver histopathology and the normal SGPT levels at the 100 mg/kg dose level. The lowest-observed-adverse-effect-level (LOAEL) was determined to be 300 mg/kg. The LOAEL was based on significant changes in the liver weight, SGPT, platelet counts, leukocyte differential shift, ALP and albumin levels, and cholesterol and glucose levels.

In an inhalation study, groups of 5 or 7 male and female Wistar rats were exposed to 0, 477 or 2,337 mg/m^3 PET for 6 hrs/day, 5 days/week for 4 weeks (Swiercz et al., 2000). Bronchoalveolar lavage (BAL) fluid was examined for viability of lung cells as well as protein and enzyme activity. All rats exposed to PET vapors for 4 weeks survived the experiment. The authors stated that clinical observations did not reveal any significant toxicological findings. The authors stated that no important changes were found in food consumption and body weight gain. Statistically significant, concentration-dependent increase in the number of total cells, as well as macrophages, polymorphonuclear leucocytes and lymphocytes were noted in BAL from male rats. No substantial changes were observed in BAL of female rats exposed to PET. Statistically significant, concentration-dependent changes n mucoprotein and activity of 13- glucuronidase and lactate dehydrogenase and were observed in BAL fluid of male and female rats. The authors stated that there was a high incidence of bronchitis and bronchopneumonia, as well as perivascular infiltration by lymphocytes in the lungs of rats exposed to 2,337 mg/m^3. The authors also stated that there were no marked pathological changes in the lungs of rats exposed to PET at a concentration of 477 mg/m^3. In the same journal article, the authors reported an RD5O (concentration of 50% decrease in respiratory rate) value of 4216 mg/m^3 (95% confidence interval of 2,795- 5,850 mg/m^3). The

NOAEL for this study was identified as 477 mg/m³. Derivation of Screening Level The only inhalation study available for review was the study by Swiercz et aI. (2000): however, this study did not assess any toxicological endpoints other than body weight, food consumption and lung pathology. Therefore, the inhalation study was determined to be inadequate for the derivation of a screening level.

The subchronic gavage study in rats (Borriston Labs, 1983) was the best study found for the derivation of a screening level. First, a reference dose was calculated according to EPA methodology (EPA, 1993).

RfD = NOAEL/(UF1 x UF2 x UF3)

Where:

UF1 = a 10-fold factor when extrapolating from valid experimental results in studies where prolonged exposure to sensitive humans is not available. This factor is intended to account for the variation in sensitivity among the members of the human population.

UF2 = a 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty involved in extrapolating from animal data to humans.

UF3 = a 10-fold factor when extrapolating from less than chronic results on experimental animals when there are no useful long-term human data. This factor is intended to account for the uncertainty involved in extrapolating from less than chronic NOAELs to chronic NOAELs.

The RfD then becomes:

RfD = (100 mg/kg)/(10 x 10 x 10)
RID = 0.1 mg/kg

In order to calculate the initial threshold screening level Rule 232(1)(b) was used as follows:

ITSL = RfD x 70kg/20m³
ITSL = 0.1 mg/kg x 70kg/20m³
ITSL = 0.35 mg/m³ x 1000µg/mg
ITSL = 350 µg/m³

According to Rule 232(2)(b) the ITSL shall have an averaging time of 24 hours. Therefore the ITSL for 4-ethyl toluene (also known as p-ethyl toluene or PET) is 350 µg/m³ (24-hr averaging time).

References

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EPA. 1993. Reference Dose (RfD): Description and Use in Health Risk Assessments. Background Document 1A, March 15, 1993. Obtained from US Environmental Protection Agency, Integrated Risk Information System (IRIS) website: http://www.epa.gov/iris/rfd.htm

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