MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

April 5, 2016

TO: File for m-tolualdehyde (CAS No. 620-23-5)

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 memo from Anne Kim dated 1/31/2006). 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.

The initial threshold screening level (ITSL) for m-tolualdehyde is 440 µg/m^3 based on an annual averaging time.

Screening Level Footnote: 20

> The combined ambient impact of meta-tolualdehyde (CAS No. 620-23-5) and para-tolualdehyde (CAS No. 104-87-0) cannot exceed the ITSL of 440 µg/m^3 with annual averaging time.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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January 31, 2006

TO: File for m-tolualdehyde (CAS #620-23-5)

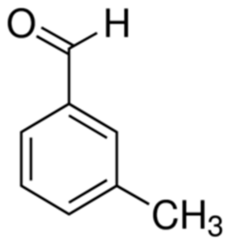
FROM: Anne Kim, Air Quality Division, Toxics Unit

SUBJECT: Screening Level Derivation

The initial threshold screening level (ITSL) for m-tolualdehyde is 440 µg/m³ based on a 24-hour averaging time.

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, Registry for Toxic Effects of Chemical Substances, American Conference of Governmental and Industrial Hygienists Threshold Limit Values, National Institute for Occupational Safety and Health Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, Chemical Abstract Service (CAS) - Online (1967 - 2004), National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. The EPA has not established a reference concentration or reference dose for m-tolualdehyde. The molecular weight of m-tolualdehyde is 120.15 g. The molecular structure of m-tolualdehyde is shown in Figure 1.

Figure 1



Background
m-Tolualdehyde is one of the three isomers of tolualdehyde: the other forms are o-tolualdehyde and p-tolualdehyde. It is used primarily as a flavoring agent in food.

Animal Toxicity In a study conducted by Brantom et al. (1972), a proportionally equal mixture of m- and p- isomers of tolualdehyde was administered via gavage to CFE-strain rats. Groups of 15 male and 15 female rats were exposed lo 0, 50, 250, or 500 mg

tolualdehyde/kg body weight/day for 13 weeks. In addition, groups of 5 male and 5 female rats were exposed to 0, 250, or 500 mg tolualdehyde/kg bwt/day for either 2 or 6 weeks. Concomitantly, two groups of 30 female rats were orally exposed to 0 or 500 mg tolualdehyde/kg bwt/day for 13 weeks to assess the effects on intestinal weight. Body weight was initially measured before the experiment and then measured every week thereafter through the length of the experiment. Intake of food and water was recorded within the 24 hours prior to each day of weighing. Urine samples were collected in the respective final weeks of treatment for analyzing the “appearance, microscopic constituents, and presence of glucose, ketones, bile salts, and blood” (Brantom et al., 1972). At the end of each experimental period, rats were fasted overnight and sacrificed under barbiturate anesthesia by exsanguination. Blood samples were collected for hematological and serum analyses. Autopsy was also performed to detect any macroscopic abnormalities and a number of organs were weighed, including the brain, heart, liver, kidneys and stomach. For the sub-study examining the small intestinal effects from treatment, the small intestine was removed at the end of treatment and weighed following a night without food.

There were no significant body weight and body weight gain differences between the treated and the control groups with the exception of the group of 5 females exposed to 500 mg tolualdehyde/kg bwt/day for 2 weeks. This group showed significantly lower body weight values compared to the control group. Except for a few significant increases in scattered values from the 2-week and 6-week studies, hematological analysis revealed no adverse effects from tolualdehyde treatment. The differences from the 2-week and 6-week studies may have been due to the small number of rats examined (5 per group). Analyses of serum samples and urine samples displayed no differences between the treated and control animals. Autopsy results revealed a non- dose-related difference in the weights of the small intestine; all treated groups had a significantly lower value compared to controls. The pituitary gland weights, when defined relative to the body weights, were significantly lower in the female rats exposed to 500 mg/kg/day in the 6-week and 13-week studies compared to control. Other differences in organ weights were observed, however, they were not consistently found nor were they found to increase in the degree of severity with increasing duration or exposure concentration. The sub-study for changes in intestinal weight showed nothing extraordinary.

The authors discussed the finding of significantly lower body weights in females exposed to 500 mg/kg/day for 2 weeks and attributed that to fortuity rather than to the effects of tolualdehyde treatment. Reasons given were, first, that there was a small number of animals in the 2-week study (5 rats per group), and secondly, the rats in the longer studies did not show these results 2 weeks into either the 6- or 13-week studies. To examine the difference in small intestine weight values, the authors cited three similar studies carried out previously, highlighting the small intestine weights of the control rats (same strain) from other studies were comparable to the treated rats in this present study. Hence, the authors concluded that the small intestine weights of the control rats in this study, for some unknown reason, were “abnormally high”. They also pointed out that since the treated rats gained weight proportionally to that of controls, the absorptive function of the small intestine was not impaired and, thus, the reduced weights are unlikely due to the effects of tolualdehyde treatment but more likely due to abnormally

high control values. The significant differences in the pituitary weight of females treated with 500 mg/kg/day, however, could not be explained. As a result, the no-untoward-effect level was determined to be 250 mg/kg/day.

In another study conducted by Vaidyanathan et al. (2003), male Sprague-Dawley rats were exposed to 50 or loo ppm of m-tolualdehyde in inhalation chambers for 6 hours. The control group was placed in inhalation chambers to simulate treatment groups, however, they were exposed only to house air. The objective of this study was to determine whether m-tolualdehyde is an active inhibitor of cytochrome P-450 (CYP) isozymes. Immediately after the 6 hours of exposure, the rats were sacrificed by carbon dioxide asphyxiation and were decapitated. Blood was collected to determine the level of m-tolualdehyde that was in circulation. Liver lobes, lung tissue, and nasal mucosa were excised to measure 3 different CYP isozyme activity: CYP 2B1, GYP 2E1, and CYP4B1.

In the lungs, GYP 2B1 activity and CYP 2E1 activity was not different from control in rats exposed to 50 ppm m-tolualdehyde (Table 1). At the 100 ppm exposure level, GYP 2B1 activity significantly decreased by 51% and CYP 2E1 activity by 24%. GYP 4B1 activity, however, increased in a dose-related manner in the lungs of rats exposed to m tolualdehyde; at 50 ppm, GYP 4B1 activity increased by 25%, and at 100 ppm, GYP 4B1 activity increased significantly by 50%. Enzyme activity in the nasal mucosa decreased significantly compared to control (Table 2). GYP 2B1 decreased by 15% after exposure to 50 ppm and 22% after exposure to 100 ppm. CYP 2E1 activity also decreased dose-dependently. There was a 37% decrease at 50 ppm and 52% decrease at 100 ppm. GYP 4B1 activity did not significantly differ from control at 50 ppm, but at 100 ppm, CYP 4B1 activity decreased by a significant 52%. Only the activity of GYP 2B1 and GYP 2E1 were tested for in the liver since CYP 4B1 produces substrates that are further metabolized by other hepatic isozymes. Analysis of the activity of the two enzymes from the liver showed no change in activity compared to control.

Table 1. Enzyme activity changes compared to control - lung

	50 ppm	**100 ppm**
CYP 2B1	-	51% decrease*
CYP 2E1	-	24% decrease*
CYP 4B1	25% increase	50% increase*

*p<0.05 significantly different from control

Table 2. Enzyme activity changes compared to control - nasal mucosa

	50 ppm	**100 ppm**
CYP 2B1	15% decrease*	22% decrease*
CYP 2E1	37% decrease*	52% decrease*
CYP 4B1	-	52% decrease*

*p<0.05 significantly different from control

Discussion

The study conducted by Vaidyanathan et al. (2003) exposed rats to 98% certified grade m-tolualdehyde. The results from the study focused on changes in three CYP isozyme activity levels in the pulmonary, nasal, and hepatic tissues. Although the biological significance of these changes is unclear, such changes in enzyme activity have historically been interpreted to indicate a normal response to the challenge rather than a toxic adverse effect. Note that the enzyme activity changes were measured in tissue not in the serum; changes in serum enzyme levels would be a toxicity-related response. The study conducted by Brantom et al. (1972) resulted in a no-observable-adverse- effect level (NOAEL) of 250 mg/kg/day based on a significant reduction in pituitary gland relative weight in female rats exposed to 500 mg/kg/day for 13 weeks. The exposure chemical was, however, not purely m-tolualdehyde; it was an equal mixture of two isomers, m-tolualdehyde and p-tolualdehyde. It is difficult to assume that these isomers are equal with regard to their toxicokinetic, toxicodynamic, and toxicological properties, since this information is not available. And while there might be a chance that the p- isomer negates the toxic effects of m-tolualdehyde exposure, it is appropriate to conservatively assume that p-tolualdehyde was not contributing to the toxicity of this mixture at all. Therefore, to derive a protective initial threshold screening level (ITSL), the conservative assumption that the significant decrease in pituitary gland weight was due to m-tolualdehyde alone will be made. The ITSL will be derived using the NOAEL of 250 mg/kg/day of the 50:50 mixture of m- and p-tolualdehyde from the Brantom et al. study.

Derivations of Screening Level

ITSL = RfD x (70 kg)/(20 m^3)
where RfD = Reference Dose

Calculation of RfD:

RfD = NOAEL/(UF1 x UF2 x UF3)
where UF = uncertainty factor

UFs that apply:

1) variation in sensitivity among members of the human population = 10
2) extrapolation from animal data to humans = 10
3) extrapolation from sub-chronic to chronic = 10

RfD = (125 mg/kg/day)/(10x10x10)
RfD = 0.125 mg/kg/day

ITSL = 0.125 mg/kg/day x (70 kg)/(20 m^3/day)
ITSL = 0.4375 mg/m^3 x 1000µg/mg
ITSL = 437.5 µg/m^3 ≈ 440 µg/m^3

Therefore, the ITSL for m-tolualdehyde (620-23-5) is 440 µg/m^3 based on a 24-hour averaging time.

References

Brantom, P.G., Gaunt. I.F., Grasso, P., Lansdown, A.B.G., Gangolli. S.D. (1972) Short-term Toxicity of Tolualdehyde in Rats. Food and Cosmetics Toxicology. 10: 637-647.

EPA. 1988. Recommendation for and documentation of biological values for use in risk assessment. PB 88-179874.

Vaidyanathan, A., Foy, J.W.-D., Schatz, R.A. (2003) Inhibition of Rat Respiratory-Tract Cytochrome P450 Isozymes Following Inhalation of m-Xylene: Possible Role of Metabolites. Journal of Toxicology and Environmental Health. Part A, 66:1133-1143.