MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

August 1, 2012

To: File for Tetrahydrofuran (CAS# 109-99-9)

From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Screening Level Updates

The Initial Threshold Screening Level (ITSL) for tetrahydrofuran (THF) is 8000 µg/m³ with annual averaging time; based on the EPA (2012) reference concentration (RfC). The Air Quality Division (AQD) ITSL of 8000 µg/m³ differs from the EPA RfC of 2000 µg/m³ because the uncertainty factor of 3 for database uncertainty was removed. The details of the ITSL calculation are shown below on page 4.

The current Initial Risk Screening Level (IRSL) of 0.5 µg/m³ is being rescinded using EPA (2012) rationale and conclusions (see below for details). A new IRSL will not be developed based on the same EPA (2012) reasoning. However, THF is considered carcinogenic based on "suggestive evidence of carcinogenic potential" following exposure to THF by all routes of exposure (EPA, 2012).

EPA (2012) decided not to develop an Inhalation Unit Risk (IUR) for THF:

> An IUR was not derived based on peer reviewers' concern for the potential overestimation of risk in deriving an IUR using a linear low-dose extrapolation approach combined with the uncertainty associated with the carcinogenic potential for THF. Because there may be some circumstances for which a cancer risk estimate for THF would be useful, EPA has presented, in Appendix B, what the inhalation cancer risk estimate would be if it were derived using a linear low-dose approach. Risk assessors should use caution when considering the use of this value due to the uncertainty associated with the potential overestimation of risk related to the linear low-dose extrapolation approach employed in its derivation and the suggestive nature of the tumorigenic response.

As EPA mentioned above, an IUR using a linear low-dose extrapolation has a degree of uncertainty and a potential for overestimating cancer risk. Still, for certain

situations a surrogate IRSL may be helpful if used with the understanding of this limitation. In an appendix of *Toxicological Review of Tetrahydrofuran* (EPA, 2012) EPA developed an inhalation cancer risk estimate based on hepatocellular adenomas or carcinomas in female B6C3F1 mice (NTP, 1998). A surrogate IRSL was developed from the IUR as follows: Surrogate IRSL = 1×10^{-6}/IUR; Surrogate IRSL = 0.33 µg/m³. This surrogate IRSL will not be placed on the screening level list, nor applied to air permits issued by the AQD at this time. Should data become available that indicates an IUR is appropriate, the AQD will review the data and update the screening level if warranted.

Details of Non-Cancer Effects and Derivation of the ITSL

A chronic RfC for THF of 2 mg/m³ was derived from data from a 105 week chronic inhalation study (NTP, 1998) in mice and rats exposed to 0, 195, 590, 1770 or 5310 mg/m³ for 6 hours/day, 5 days/week. The subchronic phase, rather than the chronic phase, of this study was selected to serve as the principal study due to comprehensive reporting in the subchronic study which better characterized the low-exposure effects associated with THF. Following 14 weeks of inhalation exposure, rats of both sexes had significantly increased relative liver weight and significantly increased relative (to body) weights for thymus and spleen; male rats also had significantly increased relative kidney and lung weights (NTP, 1998). In the same study, mice of both sexes showed increased relative liver weight and decreased relative spleen weight, while male mice only had decreased relative thymus weight and female mice had a slightly reduced relative lung weight (NTP, 1998). The subchronic toxicity study in mice (NTP, 1998; subchronic) was selected as the principal study for the derivation of the RfC. The lowest-observed-adverse-effect-level (LOAEL) was 600 ppm (1770 mg/m³) based on absolute liver weight and central nervous system (CNS) effects in male $B6C3F_1$ mile. The no-observed-adverse-effect-level (NOAEL) was identified as 200 ppm (590 mg/m³).

The EPA RfC of 2 mg/m³ was based on findings of CNS and liver toxicity in male mice (NTP, 1998), with a point of departure (POD) of 246 mg/m³ derived from the benchmark concentration[1] ($BMCL_{10}$) value for increased absolute liver weight. The POD/$BMCL_{10}$ of 246 mg/m³ was already duration adjusted based on exposure 6 hours/day, 5 days/week. The unadjusted $BMCL_{10}$ would be 1378 mg/m³ (i.e., 246 mg/m³ multiplied by 24/6 x 7/5), compared to the LOAEL of 1770 mg/m³ and NOAEL of 590 mg/m³.

EPA used a total uncertainty factor (UF) of 100. This factor was based on a default factor of 10 to account for intrahuman variability, 3 for extrapolation from an animal study for which effect levels were adjusted by appropriate animal-to-human

[1] Benchmark Concentration $BMCL_{10}$ represents the 10% extra risk using the 95% lower bound at that level.

dosimetry, and 3 to account for uncertainties in the overall inhalation toxicity database deficiency.

Concerning the uncertainty factor used for the incomplete database for THF, the EPA stated:

> Although chronic toxicity studies (NTP, 1998) and developmental toxicity studies (Mast et al., 1992; DuPont Haskell Laboratory, 1980) were available for the inhalation route, no multigeneration reproductive toxicity study by the inhalation route is available. Both the inhalation developmental toxicity studies (Mast et al., 1992; DuPont Haskell Laboratory, 1980) and the oral two-generation reproductive toxicity study (Hellwig et al., 2002; BASF, 1996) show that effects in fetuses and pups occur at exposures that cause at least minimal maternal effects and that these concentrations are higher than the NOAEL for organ weight changes in mice (NTP, 1998).

A database uncertainty factor is not typically used by the Air Quality Division (AQD) toxicologists when deriving a screening level. EPA seems to employ the database uncertainty factor in this case because there is no inhalation two-generation reproductive toxicity study. However, there is an oral two-generation study which "show that effects in fetuses and pups occur at exposures that cause at least minimal maternal effects and that these concentrations are higher than the NOAEL for organ weight changes in mice." EPA cites NTP 1998, which is an inhalation study, thus comparing doses from a two-generation oral study to a chronic inhalation study. EPA does not show the dose conversion values from oral to inhalation or inhalation to oral that would support their point. Additional information about the effects of THF on the fetuses in found here:

> The inhalation data for THF suggest that fetuses may not be more sensitive than adult animals given that the observed LOAELs for developmental effects were greater than the LOAELs for systemic toxicity (CNS and liver weight changes) in adult animals. In the oral two-generation reproductive toxicity study for THF, postnatal development (decreased pup body weight gain, in addition to delayed eye opening and increased incidence of sloped incisors) was affected at drinking water concentrations that had minimal effects on the dams.

Since the liver weight NOAEL from the chronic inhalation study is lower than the dose that produced developmental effects in fetuses, pups and dams, and that the developmental data suggest that "fetuses may not be more sensitive than adult animals", it seems unlikely that using the liver weight NOAEL would underestimate the risk from THF exposure/effects that might be observed in a multi-generation reproductive toxicity. Therefore, it was deemed as appropriate to remove the 3 fold uncertainty factor for database deficiency when calculating a screening level for

THF. Using the benchmark concentration at 10% extra risk point of departure (POD) the screening level is thus:

Screening Level = POD/UF_H x UF_A

Where UF_H = Intrahuman (10); and UF_A = Animal to Human (3)
(NOTE: dosimetric adjustment factor =1, for animal to human conversion)

Screening Level = $BMCL_{10}/(10 \times 3)$
Screening Level = 246 mg/m³/30
Screening Level = 8.2 mg/m³
Screening Level = 8,000 µg/m³

Annual averaging time was applied to the screening level because the screening level was adjusted for and based on data to account for chronic continuous inhalation exposure up to a lifetime.

Previous Screening Level

The AQD (Hultin, 2001) previously established a screening level of 18 µg/m³ based on a subchronic LOAEL of 100 ppm (295 mg/m³) identified by Katahira et al. (1982)(abstract only). EPA obtained the original Katahira study that was subsequently published by Horiguchi et al. (1984). EPA's summary of Horiguchi et al. (1984) follows:

> Horiguchi et al. (1984) evaluated the subchronic inhalation toxicity of THF in rats. Male Sprague-Dawley rats (11–12/group) were exposed to THF vapors 5 days/week, 4 hours/day for 12 weeks. Two experiments using different concentrations were conducted. THF concentrations for the first experiment were 0, 200, or 1,000 ppm (0, 590, or 2,950 mg/m3) and for the second experiment were 0, 100, or 5,000 ppm (0, 295, or 14,750 mg/m3). Body weights and clinical signs of intoxication were observed daily during the exposure period. Rats were sacrificed on the second day following termination of exposure. Blood was drawn for hematological and serum chemistry evaluation. Major organs were weighed and evaluated histopathologically. Body weight in rats exposed to 5,000 ppm was significantly lower than controls for the entire exposure period; no differences from controls were observed in the other treated groups. Animals in the 5,000 ppm group displayed signs of local irritation and CNS effects, which were described by the study authors as similar to those observed for the acute study (Horiguchi et al., 1984). These local irritation and CNS effects were reported as moderating with continued exposure. There were statistically significant increases in serum AST at exposures ≥200 ppm; however, the magnitudes of the increases were minimal and were not dependent on the exposure levels (the highest increase was 50% greater than controls at 1,000 ppm while at 5,000 ppm it only increased by 18%). Compared to the control values, the following parameters were also changed in the 1,000 and/or 5,000 ppm exposure groups. At 1,000 and 5,000 ppm, cholinesterase was slightly but significantly increased by 8 and 15%, respectively, while blood sugar was significantly decreased by 20 and 39%, respectively. Serum ALT, cholesterol, and

bilirubin were significantly increased only in the 5,000 ppm group (by 100, 44, and 46%, respectively). White blood cell count was significantly decreased (by about 24%) in the 5,000 ppm group compared with controls. Relative organ weights were significantly increased (by 7–28%) only in the 5,000 ppm group, including brain, lung, liver, pancreas, and kidney, while the relative spleen weight was decreased (by 13%). All histopathological findings were comparable between treated and control groups. Based on body weight, organ weight changes, local irritation and CNS effects, and serum chemistry parameter changes, EPA identified 5,000 ppm (14,750 mg/m3) as the study lowest-observed-adverse-effect level (LOAEL) and the no-observed-adverse-effect level (NOAEL) as 1,000 ppm (2,950 mg/m3). The results of Horiguchi et al. (1984) were also reported in an earlier Japanese publication from the same laboratory (Katahira et al., 1982).

EPA found that the 5,000 ppm (14,750 mg/m3) dose level was a LOAEL, and that the NOAEL was 1000 ppm (2950 mg/m³). In 2001 when the screening level of 18 µg/m³ was developed, the dose of 100 ppm (295 mg/m³) was erroneously identified as a LOAEL. Hultin (2001) also used a total UF of 600. The UF for LOAEL to NOAEL was 2 because the effects in the nasal epithelium were "very mild". The dosimetric adjustment factor (DAF) of 0.285 for category 1 gases was used because the critical effect was in the nose (i.e., a portal of entry effect). Recall that EPA (2012) used a DAF of 1. This indicates that the dose in animals is expected to be equal to that of human when considering pharmacokinetic and pharmacodynamic characteristics.

Other Considerations for Screening Levels: Occupational Exposure Limits

The EPA has not derived an Acute Exposure Guideline Level (AEGL) for THF, nor has a provisional peer-review toxicity value (PPRTV) been developed. The American Conference of Governmental and Industrial Hygienists (ACGIH) derived a Threshold Limit Value (TLV) for THF of 50 ppm (150 mg/m³) based on upper respiratory tract irritation, central nervous system (CNS) impairment and liver cancer. The ACGIH also derived a short term exposure limit (STEL) of 100 ppm (300 mg/m³). The National Institute for Occupational Safety and Health (NIOSH) derived a Recommended Exposure Limit (REL) of 200 ppm (590 mg/m³).

A potential screening level based on an occupational exposure limit (OEL) was considered to account for short-term exposures. The ACGIH TLV of 150 mg/m³ was the lowest OEL. Pursuant to Rule 232(1)(c):

Short-term Screening Level = OEL/100

Short-term Screening Level = 150 mg/m³/100

Short-term Screening Level = 1.5 mg/m³

Rounding to 1 significant figure and converting to micrograms yields:

Short-term Screening Level = 2000 µg/m³

ITSLs based on OELs are given 8-hr averaging times. Normally a secondary ITSL would be developed for short-term high exposures. However, the primary ITSL of 8000 µg/m³ with an annual averaging time would be greater than the short-term ITSL of 2000 µg/m³ based on the OEL. Typically a short-term ITSL would be higher than the long-term or chronic ITSL. Since the opposite would occur in this instance, a secondary short-term ITSL was not developed.

Cancer

The available mechanistic information and possible modes of action were evaluated for the male rat kidney tumors and female mouse liver tumors. For the rat kidney tumors, there were some data suggesting that following the inhalation exposure in the NTP (1998) bioassay, tumors developed due to the accumulation of α_{2u}-globulin. However, the data were insufficient to establish this mode of action. Also, the available evidence is not sufficient to support chronic progressive nephropathy (CPN) as a potential mode of action (MOA) for the increase in male rat kidney tumors. For mouse liver tumors, although increased cell proliferation was noted in short-term studies and showed the expected temporal relationship at early time points, these data were not adequate to establish this MOA. The absence of a significant increase in cell proliferation in tissues obtained from the subchronic NTP (1998) study also suggests that cell proliferation might not be a sustained response even with continued dosing. Furthermore, key precursor events linked to observed cell proliferation were not identified. It is not clear that the cell proliferation effect was sustained for a sufficient duration to adequately explain the late onset of tumors. The data on other potential modes of action were too limited to establish the MOA for liver tumors induced by THF. The U.S. EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005) state: "When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the nature of the data generally would not support one.

Additional information concerning EPA's reasoning for not deriving a quantitative risk value for THF can be found here:

> A majority of the external peer review panel members (see Appendix A: Summary of External Peer Review and Public Comments and Disposition) stated that derivation of an inhalation unit risk (IUR) for THF would result in an overestimation of cancer risk if a linear low-dose extrapolation approach was utilized. Although the reviewers agreed with EPA's conclusion that based on the available data the modes of action for both liver and kidney tumors induced by THF are not well understood, they suggested that THF is a weak, nongenotoxic carcinogen that would have a threshold. Specifically, they stated that THF does not appear to be genotoxic, does not produce irreversible damage and/or proliferative lesions that are preneoplastic, is rapidly metabolized, and is not bioaccumulative, and thus recommended the use of a nonlinear extrapolation approach to quantify cancer risk for THF. The reviewers who recommended a nonlinear approach suggested that a

nongenotoxic carcinogen would consequently have a nonlinear cancer response at low dose. This concept is recognized as controversial in the scientific community.

If data were available to better inform the mode of action, and the data were indicative of a threshold response, then a reference value could be derived based on a precursor endpoint (i.e., key event in the mode of action) and considered for the RfC for THF. In such a case, the reference value would be considered protective against tumor development following inhalation exposures. For THF, there were no reported noncancer effects that could serve as a precursor endpoint upon which to base a nonlinear analysis. EPA considered whether the cell proliferation reported in the livers of mice following short-term exposure to THF was a potential key event in the development of female mouse liver tumors; however, given the absence of proliferation data in any of the subchronic or chronic studies, the use of this endpoint is not supported. Thus, the nonlinear analysis recommended by the peer reviewers cannot be readily implemented.

If mechanistic data becomes available that supports the use of either a threshold (cell proliferation as cancer precursor) or non-threshold (genetic dysregulation), then a quantitation of cancer risk can be made.

References

BASF. (1996) Tetrahydrofuran: two-generation reproduction toxicity study in Wistar rats, continuous administration in the drinking water, with cover letter dated 8/30/96. Study No. 71R0144/93038. Submitted under TSCA Section 8D. EPA Document No. 86960000573. NTIS No. OTS558774.

DuPont Haskell Laboratory. (1980) Tetrahydrofuran (THF) inhalation: effect on the rat conceptus. E.I. DuPont de Nemours and Company, Newark, DE; HLR-750-82. Submitted under TSCA Section 8ECP; EPA Document No. 88-920001524; NTIS No. OTS0535908.

EPA. (2005) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001B. Available from: <http://www.epa.gov/iris/backgrd.html>.

EPA. (2012) Toxicology Review of Tetrahydrofuran (CAS No. 109-99-9). In Support of Summary Information on the Integrated Risk Information System (IRIS). February 2012. EPA/635/R-11/006F.

Hellwig, J; Gembardt, C; Jasti, S. (2002) Tetrahydrofuran: two-generation reproduction toxicity in Wistar rats by continuous administration in the drinking water. Food Chem Toxicol 40(10):1515–1523.

Hultin, Mary Lee. (2001). Memo. To: File for Tetrahydrofuran (CAS#109-99-9). From: Mary Lee Hultin, Toxics Unit, Air Quality Division. Subject: Screening Level Tetrahydrofuran (CAS#109-99-9). Dated: December 21, 2001. Interoffice Communication, Michigan Department of Environmental Quality.

Mast, TJ; Weigel, RJ; Westerberg, RB; et al. (1992) Evaluation of the potential for developmental toxicity in rats and mice following inhalation exposure to tetrahydrofuran. Fundam Appl Toxicol 18(2):255–265.

NTP. (1998) Toxicology and carcinogenesis studies of tetrahydrofuran (CAS No. 109-99-9) in F344/N rats and B6C3F1 mice. Public Health Service, U.S. Department of Health and Human Services; NTP TR- 475. National Institute of Environmental Health Services, Research Triangle Park, NC