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September 15, 2017

Response to Public Comments for Tetrahydrofuran (CAS No. 109-99-9)

Summary:

Based on public comments, the Air Quality Division (AQD) has reviewed the human carcinogenicity potential of tetrahydrofuran (THF). AQD does not currently regulate THF as a carcinogen with an Initial Risk Screening Level (IRSL) and Secondary Risk Screening Level (SRSL). AQD agrees with the commenter that, despite evidence of carcinogenicity in two animal species, these findings are not relevant to human risk assessment. It would not be appropriate to derive a cancer unit risk estimate or to regulate THF as a carcinogen with an IRSL and SRSL.

Background:

Revisions to the Air Pollution Control Rules[1] were promulgated December 22, 2016. Subsequently, the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) published toxic air contaminant screening levels and their basis as required by Rule 230(1). Pursuant to Rule 230(2), the AQD solicited and received public comments on these screening levels for 60 days: February 14 through April 14, 2017. The AQD must respond to these comments within 180 days; the latest date for response is October 11, 2017.

[1] Air Pollution Control Rules in Michigan Administrative Code promulgated pursuant to Article II Pollution Control, Part 55 (Sections 324.5501-324.5542), Air Pollution Control, of the Natural Resources and Environmental Protection Act, 1994.PA 451, as amended (NREPA).

Comments and Responses:

Comment: The Tetrahydrofuran (THF) Task Force, representing U.S. manufacturers and users of THF, disagrees with the statement in the MDEQ August 2012 Screening Level Update memorandum that THF is considered carcinogenic. MDEQ should be aware that THF has not been listed as a human carcinogen by any authoritative regulatory body. MDEQ should be very cautious in its justification documentation to avoid the indication that THF may be a carcinogen in humans, as that is not supported by the current regulatory status.

Response: AQD's screening level memo correctly states that the U.S. Environmental Protection Agency (U.S. EPA, 2012) found that THF has "suggestive evidence of carcinogenic potential" by all routes of exposure. Recently, the International Agency for Research on Cancer (IARC, 2017) identified THF as, "Possibly Carcinogenic to Humans" and "Group 2B" (Gross et al., 2017). Also, a plain reading of Rule 103(c)[2] would incline AQD to deem THF as a carcinogen, since subrule (iii) of the "carcinogen" definition states:

> Group C - - Any substance for which there is limited evidence of carcinogenicity in animals in the absence of human data and which causes a significant increased incidence of benign or malignant tumors in a single, well-conducted animal bioassay.

Nevertheless, as stated in the AQD screening level memo, it is not appropriate to derive an inhalation unit risk for THF or to regulate it as a carcinogen with an IRSL and SRSL.

Comment: There are several publications concerning the findings from the THF rat cancer studies, the associated tumor formation, and chronic progressive nephropathy (CPN) that are not referenced in the August 2012 MDEQ memorandum, including:

1. Hard, G.C. et al. (2013). *Consideration of Rat Chronic Progressive Nephropathy in Regulatory Evaluations for Carcinogenicity*. Toxicol. Sci. 132(2):268-275.
2. Fenner-Crisp, P.A., Mayes, M.E., David, R.M.. (2011). *Assessing the human carcinogenic potential of tetrahydrofuran: I. Mode of action and human relevance analysis of the male rat kidney tumor.* Reg. Toxicol. Pharmacol. 60:20-39.

As noted in the Hard publication and other available literature, CPN is distinct to rats with no counterpart in human disease; therefore, tumor formation in rats as a result of CPN, which is the case with THF, has no relevance for human risk assessment. In addition, the THF Task Force has engaged in comprehensive research concerning the mode of action (MOA) for cancer effects seen in mice, and whether the MOA is relevant for humans. That research is complete and supports a conclusion that the mouse tumor formations are also not relevant for human risk assessment. The research work will be published within the next few months and should be critical in MDEQ's final assessment for THF.

[2] Rule 103(c) "carcinogen". Air Pollution Control Rules in Michigan Administrative Code promulgated pursuant to Article II Pollution Control, Part 55 (Sections 324.5501-324.5542), Air Pollution Control, of the Natural Resources and Environmental Protection Act, 1994.PA 451, as amended (NREPA).

Response: AQD reviewed the research presented by Hard, G.C. et al. (2013), and Fenner-Crisp et al. (2011), as well as a recent publication by Choi et al., (2017) that was referenced in the comments but not explicitly cited[3]. A plausible MOA for THF-induced male rat kidney tumors observed in NTP (1998) involves the accumulation of alpha-2u globulin, chronic progressive nephropathy and results in male rat kidney tumors. The male rat kidney response to chemicals that induce alpha-2u globulin accumulation is not relevant to humans for purposes of risk assessment (US EPA, 1991). It is reasonable to conclude that THF-induced female mouse liver tumors result from a MOA that is specific to mice, and not humans. The study by Choi et al. (2017) found that THF activates the Constitutive Androstane Receptor (CAR) in mice, which leads to altered gene expression and a subsequent increase in liver cell proliferation. CAR activation in humans does lead to cell proliferation such that the CAR-activation MOA for rodent liver tumor formation is not plausible for humans, and hence such compounds do not pose a hepatocarcinogenic hazard for humans (Elcombe et al., 2014). Therefore, AQD agrees with the commenter that the male rat kidney tumors and female mice liver tumors observed in the NTP (1998) study are not relevant for the quantitation of human cancer risk.

Summary and Conclusions:

AQD reviewed the latest research on the mode of action for THF-induced tumors in rats and mice. AQD will revise the THF screening level justification memorandum to summarize the latest research and the conclusion that the male rat kidney tumors and female mice liver tumors are not relevant for quantitation of human cancer risk. It would not be appropriate to derive a unit risk estimate or to regulate THF as a carcinogen with an IRSL and SRSL.

The primary AQD reviewer for these comments was Mike Depa, AQD Toxics Unit Toxicologist. The secondary (peer) reviewer was Robert Sills, AQD Toxics Unit Supervisor.

References:

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[3] After the closing of the public comment period on April 14, 2017, AQD contacted the commenter and asked about the "research" mentioned in the statement, "research work will be published within the next few months." The commenter provided AQD with the citation of Choi et al. (2017) published in May 2017.

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