STATE OF MICHIGAN
DEPARTMENT OF ENVIRONMENTAL QUALITY
LANSING

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November 20, 2018

VIA EMAIL

Neeraja Erraguntla, Ph.D., DABT
American Chemistry Council
700 2nd Street NE
Washington, DC 20002

Dear Dr. Erraguntla:

This letter is in response to your June 29, 2018, letter *Re: Comments on MDEQ's Response to ACC's Ketones Panel's Comments on the Initial Screening Level (ITSL) and Secondary Risk Screening Value (SRSL) for Methyl Isobutyl Ketone (CAS # 108-10-1).* In your letter you state that the basis for the IRSL and SRSL for methyl isobutyl ketone (MIBK) are inappropriately based on the increased incidence rate of mononuclear cell leukemia (MNCL) in F344/N male rats.

The Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) has reviewed the information you provided in your letter, as well as in a subsequent presentation made by six of your colleagues who met with AQD toxicologists on August 23, 2018, in Lansing, Michigan. We also reviewed the available literature regarding this subject and agree that the elevated MNCL incidence rate in male F344/N rats is not relevant to human health cancer risk assessment. Therefore, the AQD is rescinding the IRSL and the SRSL for MIBK, effective today.

Please note that your comment is not part of an official public comment period regarding the screening levels for MIBK. However, the toxicologists at the AQD strive to respond to all substantive comments regarding the derivation of screening levels used to evaluate toxic air contaminants regulated pursuant to Michigan's Part 55, Air Pollution Control, of the Natural Resources Environmental Protection Act, 1994 PA 451, as amended (NREPA) (Sections 324.5501- 324.5542) and Air Pollution Control Rules (Michigan Administrative Code: R 336.1101 – R 336.1299).

The remainder of this letter provides rationale for rescinding the MIBK IRSL and SRSL based on MNCL tumors.

The animal study that forms the basis of the IRSL and SRSL was published by the National Toxicology Program (NTP) in 2007[1]. In this study NTP exposed rats and mice to MIBK for two years via inhalation resulting in increased incidences of kidney, liver and MNCL tumors. The increased incidence rates of liver and kidney tumors had previously been determined to be inappropriate to use to assess carcinogenic risk in humans.[2] The AQD used the dose-response

[1] National Toxicology Program (NTP). 2007. Technical Report on the Toxicology and Carcinogenesis Studies of Methyl Isobutyl Ketone (CAS No. 108-10-1) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Technical Report Number 538. National Institute of Environmental Health Sciences (NIEHS). U.S. Department of Health and Human Services.

[2] Response to Public Comments for Methyl Isobutyl Ketone (CAS No. 108-10-1). Michigan Department of Environmental Quality, Air Quality Division, 525 West Allegan Street, Lansing, Michigan 48909. August

data for MNCL tumors to calculate an IRSL and SRSL and published these screening levels for MIBK to AQD's on-line screening level list[3] in late 2017.

Your June 29, 2018, letter referenced two published journal articles[4] which concluded that male F344/N rats have a high spontaneous background incidence rate of MNCL, and that species-specific biology makes these tumors inappropriate models for human risk assessment. You asked for an in-person meeting with AQD toxicologists. On August 23, 2018, your colleagues presented information that supports your claim that the increased incidence of MNCL in male F344/N rats exposed to MIBK is not appropriate to use for cancer risk assessment in humans. The handouts that were shown to AQD toxicologists at this meeting summarized some of the relevant points that support this claim:

1. MIBK does not cause DNA damage
2. There have been no pre-cancerous lesions seen, including the spleen and bone marrow
3. MNCL was only seen in male rats, not seen in mice
4. IARC[5] assessment of MIBK does not mention MNCL
5. NTP stopped using F344 rats partly due to MNCL issues

The decision by the AQD to not use MNCL incidence rates in male rats to derive an IRSL and SRSL is based on cancer risk assessment guidance from the U.S. Environmental Protection Agency (USEPA).[6] The AQD used a Weight of Evidence (WOE) approach for MIBK that puts male rat MNCL tumors and the human carcinogenic potential of MIBK into the category of "*suggestive evidence for carcinogenic potential.*"[7] Specifically, we relied on the USEPA's guidance that states, "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."[8]

The finding of "suggestive evidence" in this case, depends on two factors:

1. The high background rate of MNCL in male F344/N rats
2. The incidence rate of MNCL in the high dose group male rats was only slightly statistically elevated compared to control rats

The NTP noted that the historic incidence rate of MNCL for all male control F344 rats in NTP inhalation studies is 188/399 (47.1%)[9]. The male rat high dose group had statistically elevated

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24, 2017. Available on-line: http://www.deq.state.mi.us/aps/downloads/ATSL/108-10-1/108-10-1_RTC.pdf

[3] http://www.deq.state.mi.us/itslirsl/

[4] Maronpot, R. R., Nyska, A., Foreman, J. E., Ramot, Y. (2016). The legacy of the F344 rat as a cancer bioassay model (a retrospective summary of three common F344 rat neoplasms). Critical Reviews in Toxicology, 46(8), 641-675. http://doi.org/10.1080/10408444.2016.1174669
Thomas, J., Haseman, J. K., Goodman, J. I., Ward, J. M., Loughran Jr, T. P., & Spencer, P. J. (2007). A review of large granular lymphocytic leukemia in Fischer 344 rats as an initial step toward evaluating the implication of the endpoint to human cancer risk assessment. Toxicological Sciences, 99(1), 3-19. https://academic.oup.com/toxsci/article/99/1/3/1630458

[5] The International Agency for Research on Cancer is part of World Health Organization.

[6] Guidelines for Carcinogen Risk Assessment. 2005. Risk Assessment Forum. U.S. Environmental Protection Agency. Washington, DC. EPA/630/P-03/001B

[7] Ibid, p 2-56

[8] Ibid, p 3-2

[9] NTP, p 87

(Poly-3 test P=0.027) MNCL incidence (35/50 or 70%) compared to the concurrent control rats (25/50 or 50%).[10] This difference in incidence rates between high dose and control group rats did not achieved the 1% significance level. The USEPA's cancer guidance states that, "animal bioassays presenting only one significant result that falls short of the 1% level for a common tumor should be treated with caution."[11] The significance level of MNCL was reported as 2.7%, which is above the 1% level mentioned above. Because the historic incidence rate for MNCL tumors in F344/N rats is approximately 50%, MNCL was deemed a "common tumor."

Additional support for not using the MNCL incidence rate in the F344/N male rats to derive an IRSL and SRSL comes from the fact that use of this strain of rat was discontinued in 2008 because of many problems, one of which was the high and variable incidence rate of MNCL.[12,13]

In conclusion, using the USEPA's WOE approach to interpret the human carcinogenic potential from exposure to MIBK, we conclude that MIBK has, "Suggestive evidence of carcinogenic potential." Because there is only suggestive evidence of carcinogenic potential to humans, derivation of an inhalation unit risk and subsequent calculation of an IRSL and SRSL from MNCL tumors in rats are not appropriate.

If you have any questions, please contact me at 517-284-6742; depam@michigan.gov; or MDEQ, P.O. Box 30260, Lansing, Michigan 48909-7926.

Sincerely,

Michael Depa

Mike Depa
Toxics Unit
Air Quality Evaluation Section
Air Quality Division

cc: Mr. Robert Sills, MDEQ
Ms. Doreen Lehner, MDEQ
Dr. Keisha Williams, MDEQ

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[10] Ibid, p 84
[11] Guidelines for Carcinogen Risk Assessment, p 2-20
[12] King-Herbert A, Thayer K. (2006) NTP workshop: animal models for the NTP rodent cancer bioassay: stocks and strains-- should we switch? Toxicol Pathol. 34(6):802-5.
[13] King-Herbert, AP, Sills, RC., Bucher, JR. (2010) Commentary: update on animal models for NTP studies. Toxicol Pathol. 38(1):180-1.