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Response to Public Comments for Methyl Isobutyl Ketone (CAS No. 108-10-1)

Summary:

Based on public comments, the Air Quality Division (AQD) has reviewed the Initial Risk Screening Level (IRSL) for methyl isobutyl ketone (MIBK). Because of that review, the AQD agrees with the commenter that the kidney and liver tumors produced in an animal study are not appropriate endpoints to derive an inhalation cancer potency. However, MIBK also caused a statistically and biologically significant increased incidence of mononuclear cell leukemia in male rats. Based on that finding, the IRSL and SRSL were calculated as 2 and 20 µg/m³, respectively, with annual averaging time. These replace the previous IRSL and SRSL for MIBK of 1.3 µg/m³ and 13 µg/m³.

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 Initial Risk Screening Level (IRSL) for methyl isobutyl ketone (MIBK) is inappropriate since it is based on an incorrect theoretical cancer risk. The IRSL should be eliminated based on the newly available research that MIBK-induced kidney and liver tumors occur in rodents by mechanisms that are not relevant to humans. MDEQ should conduct a weight-of-evidence analysis based on updated mode of action information.

Response: AQD (2016) calculated an inhalation unit risk (IUR) for MIBK based on a 2-year inhalation cancer study published by the National Toxicology Program (NTP) in rats and mice using the reported dose levels and the observed increases in mouse liver tumors (NTP, 2007). Multiple tumor types were produced during this study. However, kidney tumors were not used to quantitate an IUR because that tumor type in male rats was determined to occur through a mode-of-action (MOA) involving alpha$_{2\mu}$-globulin ($\alpha_{2\mu}$-g) accumulation in the male rat that is not relevant to humans (EPA, 1991). With respect to other tumor types in the male rat, EPA (1991) states that:

> Even when chemically induced $\alpha_{2\mu}$-g-related kidney tumors are present, other tumors in the male rat and any tumor in other exposed laboratory animals may be important in evaluating the carcinogenic potential of the chemical.

With respect to the comments received, liver adenomas and carcinomas in mice (NTP, 2007) were re-evaluated to determine their relevancy to MIBK human health risk assessment. The liver tumors occurred in female mice (statistically significant trend) following inhalation exposure to 450, 900, and 1,800 ppm MIBK. The increased incidence in the 1,800 ppm group was significant and exceeded the historical range for chamber controls in inhalation studies [188/399 (47% ± 10%), range 32%-66%]. The incidence of eosinophilic foci was increased in all exposed groups of female mice, and the differences from the chamber controls were significant in the 450 and 1,800 ppm groups. Eosinophilic foci consisted of enlarged hepatocytes with ground-glass appearing cytoplasm; it was reported that larger foci sometimes caused slight compression of the adjacent parenchyma. NTP (2007) reported that, “The histologic appearance of the hepatocellular proliferative lesions was consistent with those commonly observed as spontaneous lesions in mice.”

A framework for analyzing a mode of action (MOA) for MIBK induced liver tumors has been examined. The sequence of key events hypothesized includes activation of constitutive androstane receptor (CAR) which leads to the induction of cytochrome-P450 (CYP) enzymes (specifically CYP2B), hypertrophy, cell proliferation, clonal expansion resulting in foci development, and liver adenomas and carcinomas (Elcombe et al., 2014; Hughes et al., 2016). While some effects of rodent CAR activators, like phenobarbital (PB), can be observed in human liver, a major species difference is that, unlike rodents, CAR activator compounds do not increase replicative DNA synthesis in

human hepatocytes. The CAR-activation MOA for rodent liver tumor formation is expected to not be plausible for humans, and hence such compounds would not pose a hepatocarcinogenic hazard for humans, as with PB.

Some of the specific steps in this MOA include activation of CAR and induction of various cytochrome P450 isozymes ("CYP") in the liver, leading to enlarged liver cells (hepatomegaly) and increase cell division (hypertrophy) as shown by increased mitosis, leading to altered cell foci, eventually progressing to liver tumors. Evidence exists that these liver tumors arose through a receptor-mediated mechanism, resulting from the induction of cytochrome-P450 enzymes (CYP2B) that are targets of the constitutive androstane receptor (CAR).

Hughes et al (2016) investigated the MOA for MIBK-induced mouse liver tumors in male and female mice, and CAR Knockout (KO) mice. The KO mice were genetically designed and bred to remove the CAR genes. Hughes et al. (2016) exposed wild-type and CAR KO mice to either 0 or 1800 ppm MIBK for 6 h/day, 5 days/week for a total of 10 days. The mice had statistically significant increases in liver weights compared to controls that corresponded with hepatocellular hypertrophy and increased mitotic figures. Hepatocellular proliferation data indicated increased induction of DNA synthesis in wild-type mice exposed to 1800 ppm MIBK compared to control, and no increase was observed in 1800 ppm MIBK exposed CAR KO mice. MIBK induced hepatic effects are consistent with a phenobarbital-like MOA where the initiating events are activation of the CAR nuclear receptor and resultant hepatocellular proliferation leading to rodent liver tumors.

AQD found that the CAR MOA data and the conclusion of the Hughes et al. (2016) study provided a convincing explanation for MIBK induced liver tumors. Therefore, the liver tumor incidence data reported by NTP (2007) was concluded to not be appropriate to use to extrapolate to human assessment of MIBK cancer risk. Since the liver tumor endpoint was concluded not relevant to human risk assessment, these lesions will not be used to derive a health benchmark. Based on this conclusion, MDEQ is withdrawing the previously calculated IUR and IRSL based on liver tumors in mice.

There was also a positive trend in the incidences of mononuclear cell leukemia in male rats observed in the NTP (2007) study (Table 1).

Table 1. Incidences of mononuclear cell leukemia in male rats

Dose Group	Incidence	Percent Incidence
chamber control	25/50	50%
450 ppm	26/50	52%
900 ppm	32/50	64%
1,800 ppm	35/50*	70%

* statistically significant $p<0.05$

Monocellular cell leukemia incidence data from NTP (2007) was used to derive an IUR for MIBK of 4.94E-7 per µg/m³ (see AQD, 2016 for additional information regarding methodology).

Summary and Conclusion

A weight of evidence approach was used to determine that liver tumors in male mice appear to occur through a mechanism which would result in an overestimation of human liver cancer risk if a linear low-dose extrapolation approach was utilized. However, the same animal study that produced increased incidences of liver tumors in mice also produced a statistically and biologically significant increased incidence of mononuclear cell leukemia in male rats. The result of the linear low-dose extrapolation cancer model using mononuclear cell leukemia in male rats yields an inhalation unit risk (IUR) of 4.94E-7 per µg/m³. The IRSL and SRSL are calculated as 2 and 20 µg/m³, respectively with annual averaging time.

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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