MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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October 17, 2017

To: File for Methyl Isobutyl Ketone (CAS No. 108-10-1)

From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Screening Levels for Protection of Carcinogenic Risks

The Initial Risk Screening Level (IRSL) for methyl isobutyl ketone (MIBK) is 2 µg/m³ with annual averaging time.

The Secondary Risk Screening Level (SRSL) for methyl isobutyl ketone (MIBK) is 20 µg/m³ with annual averaging time.

The International Agency for Research on Cancer (IARC) evaluated the evidence that MIBK is carcinogenic to humans (IARC, 2013) and reported that there is sufficient evidence in experimental animals for the carcinogenicity of methyl isobutyl ketone. IARC put MIBK in Group 2B: Possibly carcinogenic to humans.

The National Toxicology Program (NTP, 2007) reported the results of a 2-year inhalation study in rats and mice. Groups of 50 males and 50 females of both species were exposed to methyl isobutyl ketone at concentrations of 0, 450, 900, or 1,800 ppm by inhalation, 6 hours per day, 5 days per week for 104 weeks (see Table 1).

Table 1. Exposure and Duration Adjusted Doses of MIBK in Male and Female Rats and Mice

Exposure Dose		Adjusted Dose*
ppm	*mg/m³*	*µg/m³*
0	0	0.0
450	1843	329,000
900	3687	658,000
1800	7374	1,317,000
* Exposure duration adjusted; i.e., 5days/7days x 6hrs/24hrs, and converted from mg to µg using the relationship of 1 mg = 1000 µg		

Exposure to MIBK resulted in neoplastic lesions of the kidney characteristic of alpha 2u-globulin accumulation in male rats and nephropathy in female rats. The U. S. Environmental Protection Agency (U.S. EPA, 1991) states that neoplastic lesions of the kidney associated with alpha 2u-globulin accumulation are not to be used to extrapolate cancer risks in the male rat to cancer risk in humans. Therefore the neoplastic lesions of the kidney in the male rat observed in the NTP (2007) study were not used to derive an

inhalation unit risk for MIBK. However, there were increased incidences of non-kidney tumors in male rats and male and female mice. The incidence of various tumors (other than kidney tumors) are summarized in Table 2.

Table 2. Summary of Tumor Incidence* Data from NTP, 2007

Sex, Species And Tumor	Control	450 ppm	900 ppm	1800 ppm
Male Rat Mononuclear Cell Leukemia	25/50	26/50	32/49	35/50
Male Mice Hepatocellular Adenoma	17/50	25/50	23/48	34/49
Male Mice Hepatocellular Adenoma and Carcinoma	27/50	34/50	28/48	37/49
Female Mice Hepatocellular Adenoma	13/43	15/43	20/44	23/45
Female Mice Hepatocellular Adenoma and Carcinoma	17/47	17/48	20/47	27/47

*Survival-adjusted incidence rates in all groups were calculated in order to account for death of animals before the first appearance of the tumor in treated groups.

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.

The Air Quality Division (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, Michigan Department of Environmental Quality (MDEQ) is withdrawing the previously calculated IUR, IRSL and SRSL based on liver tumors in mice derived in June 1, 2016 (AQD, 2016).

There was also a positive trend in the incidences of mononuclear cell leukemia in male rats observed in the NTP (2007) study (Table 3).

Table 3. 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	32/49	65%
1,800 ppm	35/50*	70%

* statistically significant $p<0.05$

Human Equivalent Concentrations (HECs) were calculated for MIBK according to EPA guidance (U.S. EPA, 1994) for category 3 gases by adjusting intermittent exposure levels to a continuous exposure basis and multiplying the result by a ratio of the animal blood gas partition coefficient for MIBK to the human blood gas partition coefficient [$Dose_{HEC}(mg/m^3) = Dose_{ADJ}(mg/m^3) \times (H_{b/g})_A/(H_{b/g})_H$]. EPA guidance (U.S. EPA, 1994) indicates that the default value of the $(H_{b/g})_A/(H_{b/g})_H$ ratio should be set equal to 1 if blood:air partition coefficient data are not available for either humans or animals. As no animal blood:air partition coefficients were located, the $Dose_{HEC}$ values for MIBK were set equal to the continuous duration-adjusted exposure concentrations in all cases.

The EPA's Benchmark Dose Software (BMDS)(U.S. EPA 2013) was used to fit a curved line to the dose-response data (e.g., exposure concentration in a dose group and incidence of tumors). The BMDS calculates the 95% lower confidence limits on the slope

of the dose-response curve at the default benchmark response (BMR) of 10%. All of the available dichotomous cancer models (first, second and third degree polynomials; or k-1 where k is the number of dose groups) were run by the software. A Microsoft Excel® spreadsheet add-on called "Dragon BMDS Wizard" (hereafter the "Wizard") created by ICF International©, was used for data entry and model output (see Henning et al, 2014). Survival-adjusted incidence rates were used as input for the software in order to account for death of animals before the first appearance of the tumor. The output from the BMDS is transferred to the Wizard automatically. The Wizard output data included curved lines that adequately fit the data. The Wizard then choses a recommended model based on several factors, including Akaiki Information Criteria (AIC), and how closely the curve fits at the lowest exposure dose. Details on the viability of individual model fit and recommendation criteria are available from EPA's website https://www.epa.gov/bmds. Results from the model outputs for mononuclear cell leukemia are shown in Table 4.

Table 4. BMDS Output of Inhalation Unit Risk from Exposure to MIBK

Sex, Species And Tumor	Inhalation Unit Risk	IRSL	SRSL
male rat mononuclear cell leukemia	4.94E-07	2.0	20

The IUR of 4.94E-07 per µg/m³ was derived from the incidence rates of male rat mononuclear cell leukemia which was subsequently used to derive the IRSL and SRSL:

IRSL = 1E-6/(unit risk)
IRSL = 1E-6/(4.94E-07 per µg/m³)
IRSL = 2 µg/m³

SRSL = 1E-5/(unit risk)
SRSL = 1E-5/(4.94E-07 per µg/m³)
SRSL = 20 µg/m³

Pursuant to Rule 231(4) the averaging time is annual.

References

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INTEROFFICE COMMUNICATION

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May 31, 2016

To: File for Methyl Isobutyl Ketone file (CAS # 108-10-1)

From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Acute Screening Level with 8-hour Averaging Time

The Initial Threshold Screening Level (ITSL) for methyl isobutyl ketone (MIBK) is 820 µg/m³ with an 8-hr averaging time.

The American Conference of Governmental and Industrial Hygienists (ACGIH) derived a Threshold Limit Value – Time Weighted Average (TLV-TWA) for MIBK at 20 ppm (82 mg/m³) to protect against central nervous system (CNS) effects in occupational settings (ACGIH, 2010). ACGIH (2010) also derived a Threshold Limit Value – Short-term Exposure Limit (TLV-STEL) of 75 ppm (3100 mg/m³).

ACGIH (2010) summarized several human studies used to derive the TLV. One study found that at 200 mg/m³ (49 ppm) for two hours there was a statistical elevation in intensity of CNS symptoms as reported on the 17-item questionnaire.

In another study reported by ACGIH (2010), more than two-thirds of 19 workers were exposed to MIBK in a room with a centrifuge for 20 to 30 minutes per day. The concentration of MIBK was 500 ppm (2048 mg/m³) near the centrifuge, whereas others in the room were exposed to 80 ppm (327 mg/m³). Clinical chemistry results from all the workers were within the normal range. ACGIH (2010) reported that more than half of 19 workers involved complained of weakness, loss of appetite, headache, burning of the eyes, stomach ache, nausea, and vomiting. Four were said to have slightly enlarged livers and six complained of nonspecific colitis. A follow-up study conducted five years later identified air concentration of MIBK of 100 to 105 ppm in the vicinity of the centrifuge and 50 ppm elsewhere in the room during the operation of the centrifuge. Only one of the 14 original workers reported eye irritation at the five year follow-up interview. A few workers still complained of gastrointestinal and CNS disturbances. Slight liver enlargement persisted in two workers, but other earlier symptoms had been reduced to the point of disappearing.

Pursuant to Rule 230(1)(c) the ITSL is calculated as follows: ITSL = OEL/100

ITSL = 82 mg/m³/100 x 1000µg/mg = 820 µg/m³

Where the OEL is the occupational exposure limit, in this case the OEL is the ACGIH TLV-TWA.

Reference

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