**MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY**

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**INTEROFFICE COMMUNICATION**

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June 1, 2016

To: File for Methyl Isobutyl Ketone file (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 1.3 µg/m³ with annual averaging time.

The Secondary Risk Screening Level (SRSL) for methyl isobutyl ketone (MIBK) is 13 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 Adenoma | 17/50 | 25/50 | 23/48 | 34/49 |
| Male Mice Adenoma and Carcinoma | 27/50 | 34/50 | 28/48 | 37/49 |
| Female Mice Adenoma | 13/43 | 15/43 | 20/44 | 23/45 |
| Female Mice 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.

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)(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 each tumor are shown in Table 3.

**Table 3. 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 |
| Male Mice Adenoma | 7.65E-07 | 1.3 | 13 |
| Male Mice Adenoma and Carcinoma | 7.10E-07 | 1.4 | 14 |
| Female Mice Adenoma | 4.94E-07 | 2.0 | 20 |
| Female Mice Adenoma and Carcinoma | 4.70E-07 | 2.1 | 21 |

BMDS modeling of the male mice hepatocellular adenomas generated the highest cancer potency (i.e., Inhalation Unit Risk) resulting from exposure to MIBK. Using the male mice hepatocellular adenomas to derive the IRSL and SRSL results in the lowest IRSL, and therefore, would safeguard against the occurrence of the other cancers resulting from exposure to MIBK. The IUR

of 7.65E-07 per µg/m³ for hepatocellular adenomas in male mice was used to derive the IRSL and SRSL pursuant to Rule 231(1) as follows:

IRSL = 1E-6/(unit risk)
IRSL = 1E-6/(7.65E-07 per µg/m³)
IRSL = 1.3 µg/m³

SRSL = 1E-5/(unit risk)
SRSL = 1E-5/(7.65E-07 per µg/m³)
SRSL = 13 µg/m³

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

**References**

Henning (Cara), A.J Overton, Ross Pam, Audrey Turley, Joshua Cleland (2014) Benchmark Dose Wizard. (2014) Version 1.9 Updated 05/22/14. BMDS Wizardv1.9-dichotomous-cancer.xlsm ICF International, Inc.© 9300 Lee Highway, Fairfax, VA. www.icfi.com

IARC (2013) Some Chemicals Present in Industrial and Consumer Products, Food and Drinking-water. Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer. Volume 101 page 305-323.
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NTP (2007) National Toxicology Program (NTP) 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) National Toxicology Program P.O. Box 12233 Research Triangle Park, NC 27709 February 2007 NTP TR 538 NIH Publication No 07-4476 National Institutes of Health Public Health Service. U.S. Department Of Health And Human Services. NTP is part of the National Institutes of Health (NIH).
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U.S. EPA (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F.

U. S. EPA (2013) Benchmark Dose Software (BMDS) Version 2.4 R70 [Build: 04/01/2013]. National Center for Environmental Assessment. Developed for EPA by Lockheed Martin Corp. Available from: http://www.epa.gov/NCEA/bmds/index.html(Accessed 02/01/2013).

U.S. EPA (2014) Benchmark Dose Software (BMDS) Version 2.5.0.82 [Build: 5/17/2014]. National Center for Environmental Assessment. Available from: http://www.epa.gov/NCEA/bmds/index.html

**MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY**

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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**

ACGIH 2010. Methyl Isobutyl Ketone. Documentation of the Threshold Limit Values and Biological Exposure Indices, 7th Edition. Cincinnati, OH.

**MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY**

INTEROFFICE COMMUNICATION

May 1, 2003

TO: Methyl Isobutyl Ketone file (CAS # 108-10-1)

FROM: Gary Butterfield

SUBJECT: Screening level for MIBK

The ITSL for methyl isobutyl ketone (or MIBK) is being updated to be based on the April 2003 EPA RfC. The RfC is based on the rat and mouse inhalation development toxicity study reported by Tyl et al (1987).

Some of the details on how the RfC was calculated follow. The Tyl et al study found reduced fetal body weights, increased skeletal variations, and increased fetal mortality at exposures of 3000 ppm (or 12292 mg/m$^3$). The NOAEL from this study is 1000 ppm (or 4106 mg/m$^3$). Calculation of the RfC was by the following method, NOAEL x 6/24 = NOAEL(adj) = NOAEL(hec) = 1026 mg/m$^3$. The MIBK is considered to be a category 3 gas, where the blood:gas partitioning is unknown. Therefore the default value of 1 is applied to the NOEAL(adj) to obtain the NOAEL(hec). An UF of 300 was applied to the NOAEL(hec) to obtain the RfC of 3 mg/m$^3$. For additional details see the IRIS printout.

The ITSL is being set at 3000 µg/m$^3$ with 24 hour averaging based on R232(1)(a).

References

EPA. 2003. Integrated risk information system (IRIS) report # 0173 for methyl isobutyl ketone (CAS # 108-10-1).

Tyl et al. 1987. Developmental toxicity evaluation of inhaled methyl isobutyl ketone in Fischer 344 rats and CD-1 mice. Fundam. Appl. Toxicol. 8:310-327.