MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Methyl Hydrazine (CAS # 60-34-4)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: Methyl Hydrazine ITSL change in the averaging time from 24 hrs to annual

DATE: December 29, 2015

The current ITSL for Methyl Hydrazine (0.03 ug/m^3) was derived on May 15, 2008 (see attached justification memo). The averaging time (AT) assigned to the ITSL at that time was 24 hours, as per the default methodology at that time (Rule 232(2)(b)). The current file review concludes that the AT may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is being changed from 24 hours to annual at this time.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Methyl Hydrazine (CAS No. 60-34-4)

FROM: Margaret Sadoff and Michael Depa, Toxics Unit
Air Quality Division*

DATE: May 15, 2008

SUBJECT: Development of Screening Level for Methyl Hydrazine (MH)

The initial risk screening level (IRSL) for methyl hydrazine is 8.7 x10^{-03} ug/m3 (annual). The initial threshold screening level (ITSL) is 0.03 ug/m3 (24-hour).

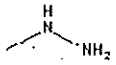
**Note: M. Depa did the initial literature search and write-up in 2001. M. Sadoff updated the literature search and memo to file document, adding the BMDS evaluation in 2007.*

A search of the literature and the following databases was performed for information regarding methyl hydrazine: American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values, National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, EPA Integrated Risk Information System (IRIS), EPA High Production Volume Information System, Registry of Toxic Effects of Chemical Substances (RTECS), Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, CAS Registry Online, Hazardous Substance Data Bank (HSDB), National Library of Medicine/Toxline, National Library of Medicine ToxSeek, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Study Database, Entrez PubMed, Scirus, IPCS Intox Databank and CalEPA's Toxicity Values Database.

Physical Properties and General Information
(Sources: NIOSH, EPA Hazard Summary (rev. Jan 2000)

MH is a clear, colorless liquid with a boiling point of 190°F and a vapor pressure of 38 mmHg. It is a highly flammable liquid with an ammonia-like odor. The odor threshold is 1 to 3 ppm (~2 to 6 mg/m^3). MH is primarily used as a component of military fuel as a rocket propellant and as a fuel for thrusters and small electrical power generating units. It is naturally occurring in certain poisonous mushrooms and can be fatal if ingested (hepatic necrosis). MH has also been used a cancer drug for treatment of Hodgkin's disease and malignant melanoma.

Figure 1. Molecular Structure of Methyl Hydrazine



MW = 46 g/mol
1ppm=1.89 mg/m3

Acute & Subchronic Toxicity

Methyl hydrazine is highly corrosive and irritating to the skin, eyes, and mucous membranes of the respiratory system. Acute inhalation exposure to high levels of methyl hydrazine may cause lacrimation, eye redness, nasal and respiratory irritation, headache, malaise, vomiting, diarrhea, ataxia, anoxia, cyanosis, tremors, and convulsions (EPA, 2000). The only description of human exposure in the literature is irritation of the eyes and nose after a 10-minute exposure to 90 ppm (170 mg/m^3) MH. Acute exposure to methyl hydrazine in humans has also been observed to affect the blood, kidneys, and liver.

Reported LC50s are as follows (RTECs):

Mice (4-hour)	56 ppm	(106 mg/m^3)
Rats (4-hour)	34 ppm	(64 mg/m^3)
Dogs (1-hour)	96 ppm	(181 mg/m^3)
Monkey (1-hour)	82 ppm	(155 mg/m^3)
Hamster/Guinea Pig (4-hour)	143 ppm	(270 mg/m^3)

Lowest reported lethality in non-human primate (monkey) (RTECs):

10 min.	16 ppm	30 mg/m^3
30 min.	5.5 ppm	10 mg/m^3
1 hour	2.7 ppm	5 mg/m^3
4 hour	0.68 ppm	1.3 mg/m^3
8 hour	0.34 ppm	0.6 mg/m^3

Chronic Toxicity

The EPA Integrated Risk Information System (IRIS) has not published a reference concentration (RfC) or reference dose (RfD) for methyl hydrazine, nor any cancer potency values. However, the EPA's HEAST (1993) lists a cancer oral slope factor (human q_1*) of 1.1E+0 (mg/kg/day)$^{-1}$ based on liver tumors in hamsters. Under the Clean Air Act Amendments of 1990 (CAAA, 1990), methyl hydrazine is a Hazardous Air Pollutant (HAP).

Chronic inhalation exposure to methyl hydrazine has been observed to impair function of the kidneys and liver, affect the blood and spleen, and cause convulsions in animals. No data is available on chronic effects in humans. The morphology of sperm has been reportedly observed in mice orally exposed to methyl hydrazine. Also, an oral exposure of female rats to 5 mg/kg MH, 6 days after conception resulted in pre-implantation mortality. Neither the EPA nor

IARC has classified MH for carcinogenicity. In mice, chronic inhalation exposure to methyl hydrazine (Kinkead et al., 1985) caused adenomas and ademomatous polyps in the nasal mucosa, as well as significant increases in primary lung and liver tumors. Increases in lung tumors have also been observed in mice exposed orally to MH (by gavage and in drinking water).

The table below lists the results of some longer-term inhalation studies as reported in RTECs:

Species	Duration	Dose	Effect
Rat	24hr cts, 26 wk	0.1 ppm (0.378 mg/m3)	Metabolic-decreased weight gain
Mouse	6/24 hrs, 26 wk	5 ppm (9.5 mg/m3)	Lethargy
Dog	24hr cts, 30 wk	0.2 ppm	Blood (hemolysis)-methemoglobinemia, carboxyhemoglobin
Dog	24hr cts, 26 wk	0.2 ppm	Blood- changes in RBCs, bone marrow
Primate – Monkey	6/24 hrs, 26 wk	5 ppm	Blood changes unspecified
Rat	6/24 hrs, 1 year	0.02 ppm (0.038 mg/m3)	Blood - leukemia
Mouse	6/24 hrs, 1 year	2 ppm (3.8 mg/m3)	Liver tumors
Hamster	6/24 hrs, 1 year	5 ppm	Olfactory tumors

Occupational Exposure Limits

The 2006 ACGIH TLV booklet lists a TLV-TWA of 0.01 ppm (~20 µg/m^3) and gives methyl hydrazine an A3 designation (animal carcinogen) and a SKIN notation. Critical effects listed are upper respiratory tract irritation, lung cancer, eye irritation, and liver damage. NIOSH has set a Ceiling REL at 80 ug/m^3 (2-hour limit) and OSHA has a ceiling PEL of 350 ug/m^3 with a skin notation. The IDLH value is 20 ppm (38 mg/m^3).

Emergency Values: 1 ppm = 1.89 mg/m^3

	10 min	30 min	60 min	4 hr	8 hr
AEGL-1	not recommended due to insufficient data				
AEGL-2 (ppm)	5.3	1.8	0.90	0.23	0.11
AEGL-3 (ppm)	16	5.5	2.7	0.68	0.34

TEEL-0 = 0.01 ppm

Mutagenicity/Genotoxicity and Carcinogenicity

In vitro evidence for mutagenicity is equivocal. Positive results were reported in 4 out of 15 Ames tests and 3 out of 4 tests for chromosomal aberration. According to EPA's proposed framework for mutagenic mode of action (Sept. 2007), in order for a chemical to be classified as mutagenic there should be support from positive mutagenicity tests *in vivo* and *in vitro* as well as evidence that some mutagenic event precedes cytotoxicity and tumor formation. Therefore, MH does not meet the EPA definition of a mutagen for risk assessment purposes. There is, however, clear evidence of carcinogenicity in animals.

Supporting Studies for Carcinogenicity

(Toth B, 1972) 50 M/F **Swiss mice** were administered 0.01% MH in drinking water for life (from about the age of 6 weeks). This equated to about 0.71 mg/day MH for females and 0.66 mg/day for males. Methyl hydrazine appeared to shorten survival in Swiss mice. Females and males survived to weeks 70 and 80 respectively, as compared to controls who survived out to 120 weeks. Similarly, mice exposed to hydrazine and methyl hydrazine sulfate also survived out to 120 weeks. During the study 12/50 female mice developed **lung adenomas**. The average latent period for these tumors was 51 weeks (first observed at week 36 and last at week 67). 11/50 male mice developed lung adenomas with an average latent period of 51 weeks (first observed at week 39 and last at week 70). The next most common tumor type found was liver tumors (F = 9; M = 6). The authors concluded that 0.01% MH enhanced the development of lung tumors by shortening the latency period. It is difficult to draw conclusions from this study as to latency since it is not clear whether serial sacrifices were conducted or whether animals were autopsied after natural death.

(Toth B & Shimizu H, 1973) A 0.01% solution of MH was administered daily in the drinking water to 6-week old **Syrian golden hamsters** for the remainder of their lifetime. This equates to an intake of approximately 8.67 mg/kg/day for females and 6.88 mg/kg/day for males. MH treatment reduced survival (100 (F) and 110 (M) weeks compared to controls 120 (F) and 130 (M) weeks. 16/50 (32%) of the females and 27/50 (54%) of the males developed malignant histiocytomas of the **liver (Kupffer's cell sarcoma**) compared to no such lesions in controls. The average latency period for females was 70 weeks (46-92) and 78 weeks for males (47-103). This tumor type metastasized in 6 lungs, 2 lymph nodes and 2 spleens. In humans, a variant of this lesion called histiocytosis is relatively rare. There was also an 18% incidence of tumors of the cecum in females as compared to 14% in males as compared to 1% in controls.

Key Study for ITSL/IRSL Development - Kinkead et al. (1985)

In a chronic inhalation study, four animal species were exposed for 6 hours/day, 5 days/week for one year to selected vapor concentrations of methyl hydrazine (see Table 1). Mice, rats and hamsters were held for 1 year postexposure, while dogs were held for 5 years. Work from previous studies indicated that hamsters were less sensitive than rats or mice so they were not dosed at the lowest level, 0.02ppm. Hamsters in the high dose group at 5 ppm had nasal tumors which were statistically and biologically significant since these tumors are rare in aged hamsters. Mice developed statistically significant lesions at a lower dose (2.0 ppm) than did hamsters (5.0 ppm). Neither rats nor dogs developed any significant treatment related lesions.

Exposed hamsters showed pathologic changes characteristic of chronic irritation of the respiratory tract. Submucosal cysts, rhinitis, and epithelial hyperplasia increased in incidence in the exposed hamsters. Nasal tumors were present in hamsters exposed to the two higher concentrations. There were significant increases in irritation of the nasal cavity such as nasal inflammation, plasmacytosis and hemorrhage in the mandibular lymph nodes of exposed mice. Adenomas and ademomatous polyps were seen in the nasal mucosa of mice exposed to 2.0 ppm. There were significant increases in primary lung and liver tumors in female mice exposed to 2.0 ppm. No neoplastic changes were found in either rats or dogs. Table 2 shows the incidence rates of carcinogenic lesions. Non-neoplastic effects are shown in Table 5.

Table 1. Number of Animals and Their Exposure Levels from Kinkead et al. (1985)

Exposure Conc. → Species ↓	0 ppm µg/m³→	0.02 ppm 38 µg/m³	0.2 ppm 378 µg/m³	2.0 ppm 3780 µg/m³	5.0 ppm 9450 µg/m³
Fischer 344 Rats (male and female)	150	100	100	100	100
C57Bl/6J Mice (female only)	400	400	400	400	---
Golden Syrian Hamsters (male only)	200	---	200	200	200
Beagle Dogs (male and female)	4	---	4	4	---

Table 2. Significantly Elevated Cancer Incidence from Kinkead et al. (1985)

Exposure Conc. → Cancer Type ↓	0 ppm µg/m³→	0.02 ppm 38 µg/m³	0.2 ppm 378 µg/m³	2.0 ppm 3780 µg/m³	5.0 ppm 9450 µg/m³
Mouse Lung Adenoma	13/364	16/354	23/347	56/360**	
Mouse Liver combined Adenoma/Carcinoma	8/373	6/357	9/357	34/363**	
Mice Hemangioma	5/387	9/371	5/368	22/371**	
Hamster Nare Adenoma	1/90		0/177	0/180	7/177**
Hamster Adrenal Cortical Adenoma	16/191		16/173	10/172	23/176**

** Significantly different from controls ($p<0.05$)

Derivation of Initial Risk Screening Level (IRSL) by the Global 82 Method (2001 by M. Depa)

The Global 82 linearized multistage software program was used to derive the unit risk for each cancer type (see Table 3). Pursuant to Rule 231(3)(d), if the duration of the experiment (L_e) is less than the natural lifespan of the test animal (L) then the q_1* is multiplied by the adjustment factor $(L/L_e)^3$. This conversion is shown in the Lifetime Adjusted q_1* column in Table 3.

Table 3. Unit Risks Derived from Kinkead et al. (1985)

Cancer Type	Animal q_1* $(\mu g/m^3)^{-1}$	Lifetime Adjustment Factor**	Lifetime Adjusted q_1* $(\mu g/m^3)^{-1}$	Animal IRSL $(\mu g/m^3)$
Mice Lung Adenomas	2.55×10^{-4}	$(2/1)^3 = 8$	2.04×10^{-3}	4.90×10^{-4}
Mice Liver Adenomas	1.02×10^{-4}	$(2/1)^3 = 8$	8.16×10^{-4}	1.23×10^{-3}
Mice Liver Carcinomas	7.74×10^{-5}	$(2/1)^3 = 8$	6.19×10^{-4}	1.62×10^{-3}
Mice Hemangiomas	9.54×10^{-5}	$(2/1)^3 = 8$	7.63×10^{-4}	1.31×10^{-3}
Hamster Adrenal Cortical Adenomas	4.13×10^{-5}	$(2/1)^3 = 8$	3.30×10^{-4}	3.03×10^{-3}
Hamster Nare Adenomas	1.19×10^{-5}	$(2/1)^3 = 8$	9.52×10^{-5}	1.05×10^{-2}

** $(L/L_e)^3$: L = years of natural lifespan, L_e = years of experimental exposure

Mouse Lung Adenomas

The dose for mice lung adenomas was converted to the human equivalent concentration (HEC) using EPA (1994b) dosimetric equations for a category 1 gas (i.e., gases that are highly reactive and/or water soluble). The regional gas dose ratio (RGDR) for pulmonary (PU) effects was calculated by taking the ratio of ventilation rate (volume of air per time) to the surface area (SA) of the region.

$$RGDR_{PU} = [(V_E/SA_{PU})_A]/[(V_E/SA_{PU})_H]$$

Where V_E is the ventilation rate, SA_{PU} is the pulmonary surface area, $(V_E/SA_{PU})_A$ is the dose deposited in the mouse, and $(V_E/SA_{PU})_H$ is the dose deposited in the adult human. The default surface area of the pulmonary region of the mouse is $0.05m^2$ and for the human is $54m^2$ (EPA, 1994b).

The inhalation rate (I) can be substituted for ventilation rate (V_E). The inhalation rate (I) of the female B6C3F1 mouse[1] was calculated according to EPA (1988):

$$I = 1.686\ m^3/kg/day$$

Where I is the inhalation rate in m^3 per kg Body Weight per day. Multiplying the inhalation rate in m^3/kg/day by the default body weight of 0.035 kg for the female B6C3F1 mouse (EPA, 1988) results in an inhalation rate of 0.059 m^3/day. The default inhalation rate of the human is 20 m^3/day (EPA, 1994b).

The equation to calculate the pulmonary RGDR for mouse to human extrapolation then becomes:

$$RGDR_{PU} = [(V_E/SA_{PU})_A]/[(V_E/SA_{PU})_H]$$

$$RGDR_{PU} = [(0.059m^3)/(0.05m^2)]/[20m^3/54m^2)]$$

$$RGDR_{PU} = (1.18)/(0.37)$$

$$RGDR_{PU} = 3.189 \text{ or } \sim 3$$

Finally, to calculate the human IRSL the female mouse IRSL is multiplied by the $RGDR_{PU}$.

$$IRSL(human) = IRSL(mouse) \times RGDR_{PU}$$

$$IRSL(human) = (4.9 \times 10^{-4}\ \mu g/m^3) \times 3$$

$$IRSL(human) = 1.47 \times 10^{-3}\ \mu g/m^3$$

IRSL(human) ≈ 1.5×10^{-3} µg/m³ (by Global 82 method)

[1] The C57BL/6 is widely used as the genetic background for transgenic and mutant mice and is popular in the research applications of oncology, immunology and toxicology. It is used as the female parent to produce both the B6C3F1 and B6D2F1 hybrids. (http://www.taconic.com/anmodels/inc57b6.htm)

Table 4: Benchmark Dose* Evaluation (2007), Methyl Hydrazine BMDS Runs Version 1.4.1
Using Default BMR of 0.1 (10% response) & Incidence Rates from Table 2

	Tumor Types				
	Mouse Liver **Adenoma/Carcinoma	**Mouse Lung Adenoma**	Mouse Hemangiomas	Hamster Nare Adenomas	Hamster Adrenal Cortical Adenomas
BMD (ug/m3)	7929	**3092**	5030	13514	11603
BMDL (ug/m3)	4776	**2315**	4336	11087	9192
IUR	2.09×10^{-05}	**4.32×10^{-05}**	2.31×10^{-05}	9.02×10^{-06}	1.09×10^{-05}
AIC value	535	**728**	364	78	435
p-value	0.6	**0.5**	0.4	0.1	0.4

*Benchmark Dose (BMD), Benchmark Dose Software (BMDS), Benchmark Response (BMR), Benchmark Dose Lower 95% Limit (BMDL), Inhalation Unit Risk (IUR), Akaikie Information Criterion (AIC)
**Note: Liver adenoma/carcinomas were combined for BMD calculation.

The mouse lung adenoma endpoint was the most potent as evidenced by the low BMDL calculated and the steepness of the slope (approaching linear). The oral study by Toth et al. also supports the finding of lung adenomas in mice as a relevant carcinogenic endpoint (see supporting studies above). Therefore, the mouse lung adenoma endpoint will be used for IRSL development.

IRSL Calculation Using BMDs Values:
4.32×10^{-05} (IUR) x Lifetime Adjustment Factor (8) = 3.456×10^{-04}
$IRSL_{(A)} = 1 \times 10^{-06} / 3.456 \times 10^{-04} = 2.89 \times 10^{-03}$
$IRSL_{(H)} = 2.89 \times 10^{-03} \times RGDR_{PU}$ (3) $= 8.67 \times 10^{-03}$
$IRSL_{(H)} = 8.7 \times 10^{-03}$ (by BMDS method)

Non-Cancer Effects and Derivation of Initial Threshold Screening Level (ITSL)

The non-cancer effects of methyl hydrazine exposure are summarized in Table 5. The 0.02 ppm dose group is implicated in several dose-response trends in the mice. However, because the effects at higher doses were not statistically elevated, or the incidence of an effect was elevated at 0.02 ppm but not statistically different from controls, an adverse effect level at this dose was deemed to be equivocal. Because the dose-response trends were inconsistent at the 0.02 ppm dose level, it was considered a no-observable-adverse-effect-level (NOAEL). The 0.2 ppm dose was considered the lowest-observed-adverse-effect-level (LOAEL).

Table 5. Significant* Non-cancer Effects of Methyl hydrazine (Kinkead et al. 1985)

Species	0.02 ppm 38 µg/m³	0.2 ppm 378 µg/m³	2.0 ppm 3780 µg/m³	5.0 ppm 9450 µg/m³
Dogs (male and female)	Not Tested	↓RBC, ↓hemoglobin ↓hematocrit ↓alk. phos. ↑methemoglob**	↓RBC, ↓hemoglobin ↓hematocrit ↑alk. phos. ↑methemoglob ↑SGPT***	Not Tested
Rats (male and female)	↓Body Weight	↓Body Weight	↓Body Weight	↓Body Weight
Hamsters (male only)	Not Tested	↑Biliary Cysts ↑Nasal Lesions	↑Biliary Cysts ↑Nasal Lesions ↑Atelectasis ↑Nephrosis	↑Biliary Cysts ↑Nasal Lesions ↑Atelectasis ↑Nephrosis
Mice (female only)	↑Nasal Inflamm. Lymph Node Plasmacytosis	↑Liver Cysts ↑Angiectasis Lymph Node Plasmacytosis	↑Nasal Inflamm. ↑Liver Cysts ↑Bile Duct Hyper ↑Angiectasis Lymph Node Hemorrhage	Not Tested

*p<0.05, only clearly positive or negative trends are shown
**At 0.2 ppm methemoglobin was increased in serum at 6 months, but not at 3, 9 or 12 months of exposure. However, at 2 ppm, methemoglobin was increased at all 4 sampling periods.
*** Serum Glutamic-Pyruvic Transaminase

The chronic NOAEL of 0.02 ppm (37.6 µg/m³) observed in Kinkead et al. (1985) was used to derive the RfC. Nasal inflammation was not amenable to BMD modeling as there were no clear dose response relationships and the BMDS calculation failed.

NOAEL RfC Approach for Nasal Inflammation
$NOAEL_{adj}$ = NOAEL x 6/24 x 5/7
$NOAEL_{adj}$ = 38 µg/m³ x 6/24 x 5/7
$NOAEL_{adj}$ = 6.8 µg/m³
$NOAEL_{hec} - NOAEL_{adj} \times RGDR_{ET}$ $[(V_e/SA_{et})_a / [(V_e/SA_{et})_h]$*
$NOAEL_{hec}$ = 6.8 ug/m3 x $[(0.05\ m^3/3cm^2) / [(20m^3/200cm^2)]$ = ~1 ug/m3

*Methyl hydrazine was determined to be water soluble and highly irritating to the eyes and upper respiratory tract. According to EPA (1994b) it is a category 1 gas. Therefore a dosimetric adjustment is made for the differences between mice and humans in the extrathoracic space. Generic mouse parameters were used.

The uncertainty factors (UFs) used in the derivation of the RfC are 3 for interspecies, which was lowered from 10 to 3 due to use of the extrathoracic dosimetric adjustment factor (DAF), and 10 for intraspecies extrapolation, for a total of 30. The RfC was calculated as follows:

$RfC = (NOAEL_{hec})/(30)$

$RfC = (1\ \mu g/m^3)/30$

RfC = 0.03 ug/m3 (24-hour avg)

Conclusion

The **IRSL for methyl hydrazine is 8.7 x10^{-03} µg/m^3** (annual averaging time). The critical cancer effect is lung adenomas.

The **ITSL for methyl hydrazine is 0.03 µg/m^3** (24-hr averaging time). The most sensitive non-cancer chronic effect of methyl hydrazine is upper respiratory tract irritation.

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