MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Formamide (CAS # 75-12-7)

FROM: Robert Sills, AQD Toxics Unit Supervisor

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

DATE: September 8, 2015

The current ITSL for formamide (600 ug/m^3) has a justification (attached) dated July 28, 2011. The averaging time (AT) assigned at that time was 24 hours, as per the default methodology (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 Formamide (CAS # 75-12-7)

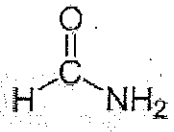
FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: July 28, 2011

SUBJECT: Screening Level for Formamide (CAS # 75-12-7)

The initial risk screening level (IRSL) for formamide (CAS # 75-12-7) is 0.2 $\mu g/m^3$ annual averaging time, while the initial threshold screening level (ITSL) for formamide is 600 ug/m^3 with a 24-hour averaging time.

Formamide (CAS # 75-12-7) also known as methanamide, carbamaldehyde, formic acid amide, and formimidic acid has a molecular weight of 45.04 and is a clear liquid, which is miscible with water and has an ammonia-like odor. It is used as a softener for paper, gums, and animal glues; as an ionizing solvent; in the manufacturing sulfa drugs and synthesizing vitamins; in water soluble inks; and in the manufacture of formic esters and hydrocyanic acid. When strongly heated, formamide decomposes to hydrogen cyanide and water vapor. The structure is shown below:



A literature review was conducted to determine an initial risk screening level (IRSL) and the initial threshold screening level (ITSL) for formamide. The following references and databases were searched to derive the above screening level: Environmental Protection Benchmark Chemical Criteria Database (EPBCCD), United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (TLV/BEI) 2010 guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), Acute Database, Chemical Abstract Service (CAS) Online (searched 4/19/11), National Library of Medicine (NLM)-online, EPA Aggregated Computational Toxicology Resource (ACToR) Database, US EPA TSCATS database, and Hazardous Substances Data Bank (HSDB).

The National Toxicology Program performed a series of gavage studies with formamide on male and female F344/N rats and male and female B6C3F1 mice over a 2-week, 3-month, and 2-year time frames (NTP TR 541). The 2-week and 3-month studies were used by NTP to determine the best dose range of formamide for the 2-year study. The 2-year study was selected as this is close to the natural life span of the animal, which allows the best extrapolation for assessing the chronic risk of cumene exposure in humans. Fifty individual female and male rats and mice were placed in groups and exposed to varied concentrations of formamide; 0 (control group), 20, 40, or 80 mg formamide/kg body weight, for 5 days per week for 104 to 105 weeks in

deionized water by gavage. At the end of the study all surviving animals were sacrificed and full necropsy and histopathology was performed. In addition to gross lesions and tissue masses, the following tissues were examined microscopically: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, eyes, gallbladder (mice), Harderian gland, heart, large intestine (cecum, colon, rectum) small intestine (duodenum, jejunum, ileum), kidney, liver, lung (with bronchus), lymph nodes (mandibular, mesenteric, mediastinal), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis (with epididymis and seminal vesicle), thymus, thyroid gland, urinary bladder, and uterus (NTP TR 541).

The NTP report on the 2-year study concluded that there was clear evidence of carcinogenic activity of formamide in male B6C3F1 mice based on increased incidences of hemangiosarcoma of the liver. An increased incidence of bone marrow hyperplasia occurred in male rats. Mineralization of the testicular arteries and tunic and hematopoietic cell proliferation of the spleen in male mice were also associated with administration of formamide (NTP TR 541). The adjusted incidence of male rat bone marrow hyperplasia was 19/50, 24/50, 22/50, and 29/50 for formamide doses of 0,20,40, and 80 mg/kg. The adjusted incidence of male mouse liver hemangiosarcoma was 1/50, 5/50, 7/47, and 8/49 for formamide doses of 0, 20, 40, and 80 mg/kg. The adjusted incidence of male mouse testicular artery mineralization was 0/50, 2/50, 5/50, and 35/50 for formamide doses of 0, 20, 40, and 80 mg/kg. The adjusted incidence of male mouse tunic mineralization was 1/50, 0/50, 5/50, and 27/50 for formamide doses of 0, 20, 40, and 80 mg/kg. The adjusted incidence of male mouse spleen hematopoietic cell proliferation was 14/50, 14/50, 20/50, and 28/50 for formamide doses of 0, 20, 40, and 80 mg/kg.

Deriving the formamide IRSL

The United States Environmental Protection Agency Benchmark Dose Software (BMDS) version 2.1.2 was used to determine an IRSL using a Benchmark Dose Response of 10% (BMR_{10}), which is a default value in the software. The software was run using dichotomous data utilizing the multistage-cancer model. The number of at risk animals was derived from the day of first incidence for liver hemangiosarcoma (day 449 of study = week 64). Table 13 (not shown here) provides the mean body weights and survival of male mice in the 2-year gavage study of formamide, the closest measurement was taken on week 65, therefore the week 65 survival rates were used as the denominator for incidence values (NTP TR 541). Using the above incidence data for liver hemangiosarcoma produced the following values: p-value of 0.4983, chi-square of 1.39, AIC of 130.875, and a multistage cancer slope factor of 0.00378395.

The multistage cancer slope factor of 0.00378395 was used as the unit risk in assessing the cancer risk screening methodology for determing an IRSL. Using the equation from Rule 231(3)(f) can be used to derive an IRSL from a 2-year gavage study using the following equation:

$$q_1^*(\mu g/m^3)^{-1} = q_1^*(mg/kg/day)^{-1} \times \frac{20m^3}{70kg} \times \frac{1mg}{1000\mu g} \times \frac{a}{b}$$

Where:
a = Absorption efficiency by inhalation route of exposure.
b = Absorption efficiency by the oral route of exposure.

Since it is unknown what the absorption efficiency of the inhalation route or the oral route, the value of 1 is substituted for both a and b. To determine q_1^* (oral slope factor), the following equation was used:

$$q_1^* animal \times T = q_1^* human$$

To determine T the following equation is used:

$$T = \left(\frac{W_H}{W_A}\right)^{1/4}$$

Where:
W_H = Average weight of an adult human and assumed to be 70 kilogram.
W_A = Body weight of male mice in kilogram.

The mean body weight for male mice at week 65 of the study was 51.5 g. Adding this information to the equation to find T above:

$$T = \left(\frac{70kg}{0.0515kg}\right)^{1/4} = 6.07187$$

For the q_1^* equation, the value for q_1^* animal is the multistage cancer slope factor of 0.00378395 in mg/kg/day from the BMDS multistage cancer model. Using the value for T calculated above in the q_1^* equation gives:

$$q_1^* human = 0.00378395\ {}^{mg}/_{kg\,/\,day} \times 6.07187 = 0.0229757\ {}^{mg}/_{kg\,/\,day}$$

Inserting the value of q_1^*human oral (mg/kg/day) into the equation to determine the q_1^* inhalation $(\mu g/m^3)^{-1}$ found in rule 231(3)(f) above gives:

$$q_1^*\left({}^{\mu g}/_{m^3}\right)^{-1} = 0.0229757\left({}^{mg}/_{kg\,/\,day}\right) \times \frac{20m^3}{70kg} \times \frac{1mg}{1{,}000\mu g} \times \frac{1}{1} = 0.000006564\left({}^{\mu g}/_{m^3}\right)^{-1}$$

Under rule 231(1) the IRSL is determined as follows:

$$IRSL = \frac{1 \times 10^{-6}}{Unit \ldots risk}$$

Where:
Unit risk = Additional lifetime cancer risk occurring in a population in which all individuals are exposed continuously for life to a concentration of 1 microgram per cubic meter of the chemical in the air they breathe.

Unit risk = q_1^*
Where:
q_1^* = Linear function or slope of the multistage model as derived in rule 231(3). This parameter is expressed in units of (microgram per cubic meter)$^{-1}$. Using the q_1^* value determined above in the IRSL equation gives:

$$IRSL = \frac{1\times10^{-6}}{0.000006564\left(\mu g/m^3\right)^{-1}} = 0.1523\,\mu g/m^3$$

After rounding to one significant figure, the IRSL is 0.2 µg/m^3. According to Rule 231(4) the averaging time for an IRSL or SRSL is annual. Therefore, the IRSL for formamide is 0.2 µg/m^3 with an annual averaging time and the SRSL is 2 µg/m^3 with an annual averaging time.

Deriving the formamide ITSL

The nonneoplastic lesions detected in the 2-year gavage study in male and female mice and rats were evaluated to determine which incidence would be used to determine an ITSL for formamide. As stated above an increased incidence of bone marrow hyperplasia occurred in male rats. Mineralization of the testicular arteries and tunic and hematopoietic cell proliferation of the spleen in male mice were associated with administration of formamide. After running the EPAs benchmark dose software version 2.1.2, which was run using dichotomous data utilizing the following statistical models at the default settings: gamma, logistic, loglogistic, logprobit, multistage, probit, Weibull, and quantal-linear. It was determined that the most critical effect from exposure to formamide was hematopoietic cell proliferation of the spleen in male mice using the logistic statistical model, which gave a p-value of 0.7555, a chi-square of 0.56, an AIC of 259.05, and a BMDL of 16.9326. Rule 232(1)(b) an ITSL can be determined using an oral reference dose. According to the EPA, dose response assessment an RfD can be determined using the following equation:

$$RfD\left(mg/kg\,day\right) = \frac{NOAEL(orLOAELorBMDL)}{UFs(UF_H \times UF_A)}$$

Where:
UF_H = intraspecies variation. A factor of 1, 3 (approximately -½log 10 unit), or 10-fold factor used to account for variation in sensitivity among members of the human population.
UF_A = interspecies variation. A factor of 1, 3, or 10 used to account for uncertainty when extrapolating from valid results of long-term studies or experimental animals to humans.

The BMDL for male mouse hematopoietic cell proliferation of the spleen was used for the numerator in the above equation:

$$RfD\left(mg/kg\,day\right) = \frac{16.9326\,mg/kg}{10\times10} = 0.1693\,mg/kg\,day$$

The equation for rule 232(1)(b) is:

$$ITSL = OralRfD \times \frac{70kg}{20m^3} = 0.1693\,mg/kg\,day \times \frac{70kg}{20m^3} = 0.5926\,mg/m^3 = 592.6\,\mu g/m^3$$

After rounding to one significant figure, the ITSL is 600 µg/m^3. According to Rule 232(2)(b) the averaging time is 24 hours. Therefore, the ITSL for formamide is 600 µg/m^3 with a 24-hour averaging time.

The initial risk screening level (IRSL) for formamide (CAS # 75-12-7) is 0.2 µg/m^3 annual averaging time, while the initial threshold screening level (ITSL) for formamide is 600 ug/m^3 with a 24-hour averaging time.

References:

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality

National Toxicology Program Technical Report Toxicology and Carcinogenesis Studies of Formamide (CAS No. 75-12-7) In F344 Rats and B6C3F1 Mice (Gavage Studies) NTP TR 541 July 2008.

DL:lh