MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

_____

INTEROFFICE COMMUNICATION

_____

TO: File for Gasoline (CAS# 8006-61-9)

FROM: Keisha Williams, Air Quality Division (AQD)

DATE: June 22, 2015

SUBJECT: Screening Level for Gasoline

The initial risk screening level (IRSL) for gasoline is 2 µg/m^3 (annual averaging time) based on the Environmental Protection Agency's (EPA's) unit risk estimate, 2.1 x 10^{-3} per ppm (EPA, 1987). The IRSL and secondary risk screening level (SRSL) were established by AQD on November 10, 2004 based on an updated determination of the molecular weight (MW) of 92 grams/mole used to calculate the IRSL (Equation 1). At this time, an updated MW estimate of 96.2 grams/mole is utilized, resulting in no change to the 2004 IRSL and SRSL.

Since unleaded gasoline is a complex mixture, its MW is most accurately described over a range of values. With the development of the first IRSL and SRSL for gasoline, the MW values considered were 66 and 108 grams/mole (MNDR, 1991), where 66 grams/mole constituted the MW of gasoline that is more in the vapor phase and 108 grams/mole constituted the MW of gasoline that is more in the liquid phase. 66 grams/mole was originally used as it gave a lower, more conservative estimate of the IRSL (MNDR, 1991). In 2004 it was decided that a MW closer to the MW used in the key study (MacFarland et al., 1984) was the most appropriate for IRSL derivation.

The specific gasoline mixture, API PS-6, was used as EPA's (1987) key study to derive the gasoline unit risk estimate of 2.1 x 10^{-3} $(ppm)^{-1}$ (MacFarland et al., 1984; ATSDR, 1995). This unit risk is based on the induction of liver tumors in female mice. 96.2 grams/mole (the MW of unleaded gasoline, API 99-01) is currently used as a surrogate for the MW of API PS-6 (EPA, 2011).

The IRSL and SRSL are calculated as shown in Equations 2 and 3.

Equation 1.
Using the conversion factor from ppm to mg/m^3 as follows:

$$ppm = \frac{\frac{mg}{m^3}\ x\ 24.45}{(mol\ wt)}$$

If MW equals 96.2 grams/mole, then 1 mg/m^3 equals 0.25 ppm.

Converting from a unit risk estimate with units of ppm to a unit risk estimate with units of µg/m^3 as follows:

$$\text{unit risk estimate} = \frac{2.1\ x\ 10^{-3}}{ppm}\ x\ \frac{0.25\ ppm}{\left(\frac{1000\ \mu g}{m^3}\right)} = 5.25\ x\ 10^{-7}\left(\frac{\mu g}{m^3}\right)^{-1}$$

Equation 2.

$$IRSL = \frac{1\ x\ 10^{-6}}{unit\ risk\ estimate} = \frac{1\ x\ 10^{-6}}{\frac{5.25\ x\ 10^{-7}}{\frac{\mu g}{m^3}}} = 1.9\frac{\mu g}{m^3} \approx 2\ \frac{\mu g}{m^3}$$

Equation 3.

$$SRSL = \frac{1\ x\ 10^{-5}}{unit\ risk\ estimate} = \frac{1\ x\ 10^{-5}}{\frac{5.25\ x\ 10^{-7}}{\frac{\mu g}{m^3}}} = 19\frac{\mu g}{m^3} \approx 20\ \frac{\mu g}{m^3}$$

References:

EPA. 1987. Evaluation of the carcinogenicity of unleaded gasoline. Office of Health and Environmental Assessment, Washington DC. PB 87 186151/AS. EPA/600/S6-87/001.

MacFarland, H.N., C.E. Ulrich, C.E. Holdsworth, D.N. Kitchen, W.H. Halliwell, S.C. Blum. 1984. A chronic inhalation study with unleaded gasoline vapor. International Journal of Toxicology 3 (4):231-248.

MDNR. 1991. Memo from Gary Butterfield to Gasoline File. Subject: Gasoline (CAS# 8006-61-9). May 31, 1991. AQD, MDNR.

ATSDR. 1995. Toxicological Profile for Gasoline. Accessed on June 22, 1015. http://www.atsdr.cdc.gov/toxprofiles/tp72.pdf.

EPA. 2011. Hazard Characterization Document: Gasoline Blending Streams Category. Accessed June 22, 2015. http://www.epa.gov/chemrtk/hpvis/hazchar/Category_Gasoline%20Blending%20Streams_December_2011.pdf.

MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

June 23, 1992

TO: Gasoline File (CAS# 8006-61-9)

FROM: Gary Butterfield

SUBJECT: Updating of the IRSL/SRSL

A CAS-on-line search of literature published since the last review, May 1991 to the present, found no new significant data that would cause the IRSL/SRSL to change. The new articles add to the continued the debate on whether epidemiology studies provide adequate evidence of gasoline's carcinogenicity. Some of the epidemiology studies do provide some additional suggestive evidence of gasolines carcinogenicity, however none of the recent studies are able to demonstrate conclusively that gasoline is a human carcinogen. Recent animal studies have focused on the issue of gasoline inducing alpha-2u-globulin renal damage followed by induction of cancer in male rats.

As none of the published research of recent articles significantly alter the reasoning and conclusions of a year ago, the IRSL and SRSL will continue to be based on the increased liver tumors observed in female mice by MacFarland et al 1984, with the resulting slope factor of 7.8 E-7 $(\mu g/m^3)^{-1}$ and an IRSL of 1.3 $\mu g/m^3$, with annual averaging.

MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

To : Gasoline File (8006-61-9) 5-31-91

From : Gary Butterfield

Subject : AAC for unleaded gasoline

Gasoline is a complex mixture containing hundreds of individual hydrocarbon chemicals within the general classes of alkanes, alkenes and aromatics. The relative amounts of the individual chemicals vary from batch to batch. This variation complicates the study of gasoline's toxic effects, as different batches potentially could exert different effects. Attempts to evaluate gasoline's toxicity are further complicated by many studies having focused on toxic effects produced by one of the individual chemical components rather than the whole mixture or total gasoline. Due to chemical interactions it is very difficult to predict the toxic effects of a complex mixture from observed effects of some of the individual components. Another factor complicating the evaluation of gasoline's toxicity is the historical timing of unleaded gasoline production. It appeared on the markets only in relative recent times compared to leaded gasoline. This point becomes important when considering epidemiology studies looking for increased occurrence of cancer. The period for human exposures to unleaded gasoline probably has not been sufficiently long for the latency period to be exceeded, therefore there has not been observable increases in tumor rates yet. For this reason, studies of leaded as well as unleaded gasoline exposure are usually taken into consideration when examining results from human studies.

Human exposure to gasoline is wide spread, including those persons pumping gasoline at self-serve stations, persons exposed to groundwater contaminated from leaking storage tanks, or persons living near a gasoline station or storage facility. Although there is wide spread exposure, the epidemiological studies conducted thus far have not been able to provide convincing evidence of gasoline's carcinogenicity to humans. However, epidemiologic studies often have difficulty in providing convincing evidence due to humans receiving multiple exposures from a wide variety of chemicals. Thus the observed effects are hard to attribute to a single specific exposure. In the case of gasoline, there has also been a great difficulty in quantifying the exposure workers have received, as well as the duration of exposure. The workers in this industry are quite mobile, not remaining at one position for an extended period of time. As a surrogate for gasoline workers, refinery workers have been used by some authors because of better defined work histories, however refinery workers are exposed to many other petroleum products other than gasoline. All of these issues contribute to the difficulties of using and interpreting epidemiology data.

There has been surprising few long-term animal studies conducted to evaluate the toxicity of gasoline when its widespread use and exposure is considered. It is generally accepted that the most appropriate study for quantitative risk assessment is a study conducted under a contract for the American Petroleum Institute (API) published by MacFarland et al (1984). In this study, rats and mice were exposed to vapors of unleaded gasoline for 2 years. This study found dose related increased incidences of male rat kidney tumors and female mouse liver tumors. The positive results reported in this study and the knowledge

that gasoline contains quantities of known carcinogens, has lead EPA to classify gasoline as a class B2 carcinogen (positive animal data and inadequate human data).

The MacFarland study has been criticized for a couple of reasons. First, the animals were exposed to total gasoline. Whole unleaded gasoline was suspended in the air, rather than only the fraction that is highly volatile (aromatics and n-paraffins or alkanes). Some critics argue that the volatile fractions don't contribute to the carcinogenicity of gasoline, and they suggest it is only the non-volatile fractions (isoparaffins or branched alkanes) which cause the carcinogenic effects. Therefore, under conditions for which humans are likely to encounter airborne gasoline, these critics contend, exposure to the carcinogenic non-volatile fractions does not occur.

A second criticism of this study, the male rat kidney tumors that were observed by MacFarland et al are similar to tumors that are peculiar to male rats and derived from alpha-2u-globulin related pathology. In 1987 EPA did not consider the alpha-2u-globulin argument as relevant for dismissing the male rat kidney tumors from use in the risk assessment process. However there have been many studies published recently that support dismissal more persuasively. The findings of MacFarland et al seem to have increased an interest in studying the effects of gasoline on alpha-2u-globulin and its association with development of the male rat kidney tumors. Among these studies, Garg et al (1988) demonstrated a dose related increase in hyalin droplet formation in the proximal convoluted tubules of the kidneys following gasoline administration. The severity of the droplet accumulation was related to the number of days of gasoline administration. This report also followed the decay in hyalin droplet numbers after exposure ceased. Following nine days of gasoline administration, the number of hyalin droplets was increased to the maximum. After three days of recovery the number of droplets had reduced to 75% of the peak. By the 12th day of recovery, the number had reached the control levels. This study provides evidence of the hyalin droplets being related to the gasoline administration. In another study with evidence of the alpha-2u-globulin mechanism contributing to the kidney tumors, Short et al (1989) was able to show there is a relationship between the amount of alpha-2u-globulin in the epithelium of the proximal tubule and the rate of cell turnover in the P2 segment of the proximal tubule.

From recent studies, it has generally been accepted that alpha-2u-globulin related male rat tumors follows the sequence of:

1) Gasoline exposure causes increased alpha-2u-globulin bound materials in the proximal tubules.
2) The alpha-2u-globulin bound materials are absorbed by cells in the tubule walls.
3) The large amount of materials absorbed cannot be digested by the normal cell mechanisms which leads to a build-up that is observable as hyalin droplets within the cells.
4) Cells are irreversibly damaged by the large number of hyalin droplets and die. Cell death causes a high rate of cell regeneration.
5) The high rate of cell regeneration leads to a greater number of spontaneous tumors being observed.

In 1991, the EPA Risk Assessment Forum examined this issue and concluded alpha-2u-globulin induced renal pathology is not an appropriate endpoint for noncancerous risk determinations, and tumors produced from this mechanism are also not an appropriate endpoint for cancerous risk assessment. It can be concluded that the gasoline induced male rat kidney tumors are inappropriate for use in risk assessment.

The incidence of female mouse liver tumors, hepatocellular adenomas and carcinomas, were also significantly increased in a dose related manner in the MacFarland et al report. The male mice had liver

tumor incidences that were approximately equal in all dose levels. The female tumors are considered to be appropriate for use to obtain a potency for gasoline. EPA (1987) conducted a quantitative risk assessment based on the incidence of hepatocell.ular carcinoma and adenomas reported by MacFarland et al (1984) in the female mice. The incidence reported was 8/57 controls, 10/52 at 67 ppm, 13/52 at 292 ppm, and 28/56 at 2056 ppm. The resultant potency from this data is 2.1 E-3 $(ppm)^{-1}$. Assuming the molecular weight of gasoline is 66, the potency can be converted to 7.8 E-7 $(\mu g/m^3)^{-1}$. The molecular weight, 66, is reported by EPA in their AP-42, within the documentation for fuel storage tanks. Note, other authors have used different estimates of molecular weight, MacFarland et al and Short et al estimate the molecular weight to be 108, while Halder et al estimated the molecular weight of 93, and ACGIH and McDermott & Killiany estimates the molecular weight to be 73. The conversion using the molecular weight of 66 is slightly more conservative than using one of the other larger molecular weights. There is little difference in the final AAC from assuming a different molecular weight (1.3 $\mu g/m^3$ or 2.1 $\mu g/m^3$ when using molecular weights of 66 or 108 respectively). The most appropriate AAC for the one in a million risk level is 1.3 $\mu g/m^3$, as based on the EPA molecular weight which is slightly more conservative.

Calculations

EPA 1987 Risk Assessment from MacFarland et al (1984) data

Male rat kidney $q_1^* = 3.5 \times 10^{-3}\ (ppm)^{-1}$

Female mice liver $q_1^* = 2.1 \times 10^{-3}\ (ppm)^{-1}$

Administered Concentration (ppm)	Duration Adjusted Concentration (ppm)[a]	Incidence (as reported in EPA 1987 and IRDC 1983)
0	0	8/57
67	11.96	10/52
292	52.14	13/57
2056	367.1	28/56

a, Lifetime adjusted concentration = administered concentration x 5 days/7 days x 6 hours/24 hours

Used Global 82 Software (Science Research Systems, Ruston , Louisiana , 1982) to verify the EPA reported slope factor (q_1^*) of 2.1 x 10^{-3} per ppm as follows:

$$q_1^* = \frac{Upper\ Conficence\ Limit}{Maximum\ Likelihood\ Estimate} = \frac{1.489\ x\ 10^{-6}}{6.962\ x\ 10^{-4}} = \frac{2.14\ x\ 10^{-3}}{ppm}$$

Calculation of acceptable ambient concentration (AAC)

Using the conversion factor from ppm to mg/m^3 as follows:

$$ppm = \frac{\frac{mg}{m^3}\ x\ 24.45}{(moelcular\ weight)}$$

If molecular weight (mol wt) equals 66 or 108 grams/mole, then 1 mg/m^3 equals 0.37 or 0.23 ppm respectively.

$$q_{1\text{when mol wt is 66}}^* = \frac{2.1\ x\ 10^{-3}}{ppm}\ x \frac{0.37\ ppm}{\left(\frac{1000\ \mu g}{m^3}\right)} = 7.8\ x\ 10^{-7}\left(\frac{\mu g}{m^3}\right)^{-1}$$

$$AAC = \frac{1\ x\ 10^{-6}}{7.8\ x\ 10^{-7}} = 1.3 \frac{\mu g}{m^3}$$

$$q^*_{1\text{when mol wt is 108}} = \frac{2.1\ x\ 10^{-3}}{ppm}\ x \frac{0.23\ ppm}{\left(\frac{1000\ \mu g}{m^3}\right)} = 4.8\ x\ 10^{-7} \left(\frac{\mu g}{m^3}\right)^{-1}$$

$$AAC = \frac{1\ x\ 10^{-6}}{4.8\ x\ 10^{-7}} = 2.1 \frac{\mu g}{m^3}$$

References :

ACGIH. 1986. Documentation of the Threshold Limit Values. Gasoline.

AP-42. 1985. EPA: Compilation of air pollution emission factors. Table 4.3-2 on page 4.3-7.

Charbonneau et al. 1987. Trace Subst Environ Health 21:263—

EPA 1991. Alpha-2u-globulin : Association with chemically induced renal toxicity and neoplasia in the male rat. Review draft - Risk Assessment Forum. SAB/SAB review draft EPA/625/3—91/019a.

EPA 1987. Evaluation of the carcinogenicity of unleaded gasoline. Office of Health and Environmental Assessment, CAG, Washington DC. PB 87 186151/AS.

Garg et al. 1988. Rapid post-exposure decay of a2u-globulin and hyalin droplets in the kidneys of gasoline treated male rats. J Toxicol Environ Health 24:145—160.

Halder et al. 1983. Renal toxicity of gasoline and related petroleum naphthas in male rats. In : Advances in modern environmental toxicology. Vol VII. Renal effects of petroleum hydrocarbons. Mehlman et al (Eds.). Princeton Scientific Publishers, Princeton NJ. pg73—88.

MacFarland et al. 1984. A chronic inhalation study with unleaded gasoline vapor. International Journal of Toxicology, 3:231-248.

McDermott & Killiany. 1978. AIHAJ 39:110.

Short et al. 1989. Elevated proliferation of proximal tubule cells and localization of accumulated a2u—globulin in F344 rats during chronic exposure to unleaded gasoline or 2,2,4-trimethylpentane. Toxicol Appl Pharmacol 101:414-431.