MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Acrylamide (CAS # 79-06-1)

FROM: Robert Sills, AQD Toxics Unit Supervisor

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

DATE: October 30, 2015

The current ITSL for acrylamide (6 ug/m^3) has a justification (attached) dated May 8, 2013. 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 Acrylamide (CAS No. 79-06-1)

FROM: Cathy Simon, Air Quality Division

SUBJECT: Screening Level Update

DATE: May 8, 2013

The initial threshold screening level (ITSL) for acrylamide is 6 µg/m^3 based on a 24-hour averaging time. The initial risk screening level (IRSL) and secondary risk screening level (SRSL) for acrylamide are 0.005 µg/m^3 and 0.05 µg/m^3, respectively, with both values based on an annual averaging time. Background information, supporting data, and the basis for these screening levels are provided below.

Initial Threshold Screening Level

In 1992, the Air Quality Division of the Michigan Department of Natural Resources (MDNR) established an IRSL for acrylamide of 0.0008 µg/m^3 (annual averaging time). At that time, no ITSL was established for acrylamide, since preliminary estimates indicated the IRSL would be significantly lower than the ITSL, and therefore an ITSL would not be necessary to limit emissions for permitting purposes (MDNR, 1992). The basis for the preliminary estimate of an ITSL was an oral reference dose (RfD) established by the U.S. Environmental Protection Agency (EPA), as no inhalation reference concentration (RfC) was available at that time.

In 2010, the EPA updated its Integrated Risk Information System (IRIS) for acrylamide, revising the oral RfD and cancer risk values, as well as adding an inhalation RfC for the first time. The inhalation RfC derived by the EPA was 6 µg/m^3, and that value remains in IRIS as of this current date (EPA, 2013).

The EPA's review of the toxicological data for acrylamide showed that there were no chronic inhalation animal studies available to derive an inhalation RfC. While the studies of occupationally exposed workers were adequate to conclude that neurological impairment was a potential health hazard from inhalation and dermal exposure to acrylamide, the data were limited in characterizing the dose-response relationship from inhalation exposure (EPA, 2010). Although adequate inhalation data were not available to derive an inhalation RfC, the EPA concluded that two chronic drinking water studies (Johnson et al, 1986; Friedman et al, 1995) used to derive the oral RfD, could also be used in derivation of the RfC.

In the study by Johnson et al (1986), groups of 90 male and female F344 rats were administered acrylamide in the drinking water at doses equivalent to 0, 0.01, 0.1, 0.5, or 2.0 mg/kg/day for two years. The critical effect identified from this study was peripheral nerve degeneration. The NOAEL for this effect was identified as 0.5 mg/kg/day, and the LOAEL as 2.0 mg/kg/day. In the Friedman et al (1995) study, male and female F344 rats were administered acrylamide in the drinking water for two years at concentrations equivalent to 0, 0.1, 0.5, and 2.0 mg/kg/day for males, and 0, 1.0, and 3.0 mg/kg/day for females. The critical

effect for this study was also peripheral nerve degeneration, with NOAELs of 0.5 mg/kg/day and 1 mg/kg/day for male and female rats respectively. The LOAELs for this effect were 2 mg/kg/day for male rats and 3 mg/kg/day for female rats.

The following justification for use of the oral studies by Johnson et al (1986) and Friedman et al (1995) to derive the inhalation RfC was provided by the EPA (2013):

> (1) a well characterized dose-response and identification of the most sensitive noncancer endpoint from an adequate database of oral exposure studies; (2) considerable evidence from occupational experience that dermal and inhalation exposures to AA [acrylamide] induce peripheral neuropathies, including development of the types of degenerative lesions observed in nerves of rats exposed via drinking water; (3) evidence of rapid, nearly complete absorption from the oral route and rapid distribution throughout the body (Kadry et al., 1999, Miller et al., 1982); (4) evidence that the elimination kinetics of radioactivity from oral or i.v. administration of radiolabeled AA [acrylamide] in rats is similar (Miller et al., 1982,); (5) similar flux of AA [acrylamide] through metabolic pathways following either single dose oral or single 6 hr inhalation exposures in rats (Sumner et al., 2003); (6) some route-to-route differences in the relative amounts of AA [acrylamide] to GA [gylcidamide], however, the differences are within two fold of each other; and (7) lack of support for portal of entry effects (EPA, 2013).

To derive the inhalation RfC, the EPA utilized the benchmark dose modeling results from the oral RfD derivation process. For this process, benchmark dose models were fit to the incidence data for degenerative nerve changes for male and female rats from the two 2-year drinking water studies (Johnson et al., 1986; Friedman et al., 1995). From these modeling data, a benchmark dose predicted to affect 5% of the population (BMD_5) was selected by the EPA, based on the results for male rats from the Johnson et al (1986) study. The BMD_5 was identified as 0.58 mg/kg/day for male rats, and the $BMDL_5$ (lower 95% confidence limit for the 5% extra risk) was 0.27 mg/kg/day. The human equivalent dose (HED) was then determined based upon pharmacokinetic models used to determine internal doses as a blood concentration based upon an area under a time-concentration curve. Based upon these models and relationships, the HED_{BMDL} was estimated to be 0.053 mg/kg/day. The HED_{BMDL} was then converted to the human equivalent concentration in air (HEC_{BMDL}), assuming a 70 kg person who breathes 20 m^3 of air per day as follows:

$$HEC_{BMDL} = HED_{BMDL} \times \frac{70\ kg}{20\ m^3\ day}$$

$$HEC_{BMDL} = 0.053\ \text{mg/kg/day} \times \frac{70\ kg}{20\ m^3\ day} = 0.18\ \text{mg/m}^3$$

The HEC_{BMDL} was used as the point of departure to determine the RfC by dividing it by a total uncertainty factor (UF) of 30, consisting of an UF_A of 3 for animal to human extrapolation, and a UF_H of 10 for human variability. This resulted in an inhalation RfC of 6 µg/m^3 as follows:

$$RfC = \frac{HEC_{BMDL}}{UF_A \times UF_H}$$

$$RfC = \frac{0.18\ mg/m^3}{3\ x\ 10} = 6\ \mu g/m^3$$

Although the EPA found the human data for acrylamide limited in characterizing the dose-response relationship from inhalation exposure, an inhalation RfC based on this data was derived to compare with that derived from the Johnson et al (1986) study. Using data from occupationally exposed workers resulted in an inhalation RfC of 2 µg/m^3. Nevertheless, because of the shortcomings of the human data, the data in animals was preferred for establishing the inhalation RfC (EPA, 2010).

No acute inhalation benchmark values established by federal agencies or organizations such as the National Academy of Sciences (NAS) Acute Exposure Guideline Levels (AEGLs) or the Agency for Toxic Substances and Disease Registry (ATSDR) minimal risk levels (MRLs) were available for acrylamide. Texas was the only state identified that has established an acute inhalation benchmark value for acrylamide. The Texas Commission on Environmental Quality (TCEQ) has established a short-term effect screening level (ESL) of 0.3 µg/m^3 (one-hour averaging time) for acrylamide. This value was derived by dividing the American Council of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value of 0.03 mg/m^3 for acrylamide by a factor of 100, resulting in a short-term ESL of 0.3 µg/m^3. The ACGIH TLV was based on data from a chronic feeding study in cats resulting in neurotoxic effects, along with consideration of the cancer potential and mutagenicity of acrylamide. Given the basis for the ACGIH TLV, it was considered not appropriate to use for establishing an acute ITSL.

Rule 232(1)(a) of the Michigan Air Pollution Control Rules specifies that if an inhalation RfC is available, the ITSL equals the RfC, and Rule 232(2)(b) provides for a 24-hour averaging time for ITSLs established by this methodology. Considering all of the above information, the ITSL for acrylamide is 6 µg/m^3 based on a 24-hour averaging time.

Carcinogenicity of Acrylamide

While the evidence for the carcinogenicity of acrylamide based on human data is considered inadequate to very limited, the evidence based on animal data is considered sufficient (IARC, 1994; NTP, 2011; EPA, 2013). The animal data supporting the finding of sufficient evidence of carcinogenicity consists of two studies using F344 rats (Johnson et al, 1986; Friedman et al 1995), and one study using F344 rats and B6C3F1 mice (NTP, 2012). All three studies utilized drinking water as the route of exposure. No animal inhalation studies were available that evaluated the carcinogenicity of acrylamide. The positive carcinogenicity bioassays by Johnson et al (1986) and Friedman et al (1995) are the same studies used by the EPA to derive the oral RfD and inhalation RfC.

As previously mentioned, Johnson et al (1986) administered acrylamide in the drinking water of male and female F344 rats for two years, at concentrations equivalent to 0, 0.01, 0.1, 0.5, and 2.0 mg/kg/day. In female rats exposed to the highest dose level, the incidence of tumors in the following tissues was significantly increased: mammary gland, central nervous system, thyroid gland-follicular epithelium, oral tissues, uterus, and clitoral gland. In male rats, the incidence of scrotal mesothelioma was significantly increased in both the 0.5 and 2.0 mg/kg/day dose groups. Additionally, the incidence of tumors of the thyroid gland-follicular epithelium was also significantly increased in male rats exposed to the highest dose level. The incidence of central nervous system tumors in male rats exposed to 2.0 mg/kg/day was significantly increased when compared to historical controls, but not concurrent controls.

In the study by Friedman et al (1995), male and female F344 rats were administered acrylamide in the drinking water for two years at concentrations equivalent to 0, 0.1, 0.5, and 2.0 mg/kg/day for males, and 0, 1.0, and 3.0 mg/kg/day for females. In male rats, the incidence of mesotheliomas of the testicular tunic and thyroid follicular cell tumors were significantly increased in the high dose group. In female rats the incidence of mammary gland tumors were significantly increased in both the mid and high dose group, while the incidence of thyroid follicular cell tumors was significantly increased only in the high dose group.

The NTP (2012) exposed male and female F344 rats and B6C3F1 mice to acrylamide in the drinking water for two years. The acrylamide concentrations in the drinking water were equivalent to 0, 0.33, 0.66, 1.32, and 2.71 mg/kg/day for male rats and 0, 0.44, 0.88, 1.84, and 4.02 mg/kg/day for female rats. For male mice, the acrylamide drinking water concentrations were equivalent to 0, 1.04, 2.20, 4.11, and 8.93 mg/kg/day, while in female mice dose equivalencies were 0, 1.10, 2.23, 4.65, and 9.96 mg/kg/day. The NTP found clear evidence of carcinogenic activity in both sexes of mice and rats. In male rats the incidences of tumors of the epididymis or testes, heart, pancreas, and thyroid were significantly increased, and in female rats tumors of the clitoral gland, heart, liver, mammary gland, oral mucosa or tongue, skin, and thyroid gland were significantly increased. In male and female mice the incidences of tumors of the haderian gland, lung, and forestomach were significantly increased. Additionally, in female mice, the incidence of tumors of the mammary gland, ovary, and skin were also significantly increased.

The International Agency for Research on Cancer (IARC) evaluated the carcinogenicity data for acrylamide, and concluded that this compound was probably carcinogenic to humans (Group 2A). This conclusion was based upon a finding of inadequate evidence in humans and sufficient evidence in animals (IARC, 1994). Of the three drinking water studies summarized above, the IARC only reviewed the Johnson et al (1985) study, but concluded the evidence in animals was sufficient based on supporting evidence as follows:

(i) Acrylamide and its metabolite glycidamide form covalent adducts with DNA in mice and rats.
(ii) Acrylamide and glycidamide form covalent adducts with hemoglobin in exposed humans and rats.
(iii) Acrylamide induces gene mutations and chromosomal aberrations in germ cells of mice and chromosomal aberrations in germ cells of rats and forms covalent adducts with protamines in germ cells of mice *in vivo*.
(iv) Acrylamide induces chromosomal aberrations in somatic cells of rodents *in vivo*.
(v) Acrylamide induces gene mutations and chromosomal aberrations in cultured cells *in vitro*.
(vi) Acrylamide induces cell transformation in mouse cell lines. (IARC, 1994, page 425).

The National Toxicology Program (NTP) lists acrylamide in the 12th edition of its *Report on Carcinogens*, concluding that acrylamide is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in animals (NTP, 2011).

The EPA has reviewed the data relevant to assessing the carcinogenic potential and concluded that acrylamide is "likely to be carcinogenic to humans" (EPA, 2013). This finding is in accordance with the EPA's 2005 *Guidelines for Carcinogen Risk Assessment*. The EPA's review of the data included the studies by Johnson et al (1986) and Friedman et al (1995), but did not include the most recent study by the NTP (2012). The basis for the EPA's conclusion regarding the carcinogenic potential of acrylamide includes the following:

> (1) chronic oral exposure of F344 rats to AA [acrylamide] in drinking water induced statistically significant increased incidences of thyroid follicular cell tumors (adenomas and carcinomas combined in both sexes), scrotal sac mesotheliomas (males), and mammary gland fibroadenomas (females) in two bioassays; (2) oral, i.p., or dermal exposure to AA [acrylamide] initiated skin tumors that were promoted by TPA in SENCAR and Swiss-ICR mice; (3) i.p. injections of AA [acrylamide] induced lung adenomas in strain A/J mice. In addition, CNS tumors were found in both of the chronic F344 rat bioassays; and (4) ample evidence for the ability of AA (primarily associated with its metabolite GA [gylcidamide]) to induce a variety of genotoxic effects in mammalian cells (EPA, 2013).

While no chronic inhalation bioassays were available to assess the carcinogenicity of acrylamide, the EPA has concluded that acrylamide is likely to be carcinogenic to humans by all routes of exposure. The basis for this conclusion comes from various studies as summarized by the EPA:

> In the case of AA [acrylamide], there is evidence of rapid, nearly complete absorption from the oral route and rapid distribution throughout the body (Kadry et al., 1999; Miller et al., 1982) and evidence that the elimination kinetics of radioactivity from oral or i.v. administration of radiolabeled AA in rats is similar (Miller et al., 1982). In addition, there is similar flux of AA [acrylamide] through metabolic pathways following either single dose oral or single 6-hr. inhalation exposures in rats (Sumner et al., 2003) and while there are some route-to-route differences in the relative amounts of AA [acrylamide] to GA [glycidamide], the differences are within two fold of each other (EPA, 2013).

The EPA has performed a quantitative cancer risk assessment for acrylamide using the data from the studies by Johnson et al (1986) and Friedman et al (1995). From the modeled results of these two studies, the EPA derived an oral slope factor of 0.5 $(mg/kg\text{-}day)^{-1}$ (EPA, 2013). This oral slope factor was based on the added risks for the increased incidence of thyroid tumors and tunica vaginalis mesotheliomas in male F344 rats from the Johnson et al (1986) study. Because no human or animal inhalation cancer bioassay data were available, and data were available as previously discussed to support route to route extrapolation, the EPA also derived an inhalation unit risk value utilizing the same study and tumor incidence data as the oral slope factor. The inhalation unit risk value derived by the EPA is 1.47×10^{-4} $(\mu g/m^3)^{-1}$, and rounded to one significant figure is 1×10^{-4} $(\mu g/m^3)^{-1}$ (EPA, 2013).

The EPA has also concluded while the exact mechanisms by which acrylamide induces cancer in animals is not fully understood, the weight of the evidence strongly supports a mutagenic mode of action. The basis for this conclusion includes several positive *in vitro* and *in vivo* genotoxicity studies for acrylamide and its epoxide metabolite, glycidamide (EPA, 2010). Because acrylamide has been identified as a carcinogen with a mutagenic mode of action, it is assumed that early life exposures (< 16 years of age) are associated with an increased susceptibility. To estimate the risk for such carcinogens, age dependent adjustment factors (ADAFs) are used to account for this increased susceptibility, consistent with the EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (EPA, 2005). This *Supplemental Guidance* provides ADAFs for the following three age groups: ADAF = 10 for <2 years; ADAF = 3 for ages 2 to <16 years; and ADAF = 1 for ≥16 years. Utilizing these ADAFs results in an adjusted inhalation unit risk ($IUR_{(Adjusted)}$) value as follows:

$$IUR_{(Adjusted)} = IUR \times \frac{2years\,x\,10 + 14\,years\,x\,3 + (54\,years\,x\,1)}{70\,years}$$

$$IUR_{(Adjusted)} = 1.47 \times 10^{-4} (\mu g/m^3)^{-1} \times 1.67 = 2.45 \times 10^{-4} (\mu g/m^3)^{-1}$$

Rounding to one significant, results in an IUR adjusted to account for a mutagenic mode of action of 2×10^{-4} $(\mu g/m^3)^{-1}$. Using the $IUR_{(Adjusted)}$ to derive the IRSL and SRSL results in the following values:

$$IRSL = \frac{1 \times 10^{-6}}{2 \times 10^{-4} \ (\mu g/m^3)^{-1}} = 0.005 \ \mu g/m^3$$

$$SRSL = \frac{1 \times 10^{-5}}{2 \times 10^{-4} \ (\mu g/m^3)^{-1}} = 0.05 \ \mu g/m^3$$

The IRSL for acrylamide is 0.005 $\mu g/m^3$ (annual averaging time), and the SRSL is 0.005 $\mu g/m^3$ (annual averaging time), derived pursuant to Rule 229(1)(c) of the Michigan Air Pollution Control Rules.

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