**MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY**

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**INTEROFFICE COMMUNICATION**

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TO: Acrylonitrile File (CAS # 107-13-1)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

SUBJECT: Screening Level for acrylonitrile (CAS # 107-13-1)

DATE: April 17, 2015

The initial threshold screening level for acrylonitrile (CAS # 107-13-1) is 2 µg/m$^3$ based on an annual averaging time. The initial risk screening level (IRSL) for is 0.01 µg/m$^3$ and the SRSL is 0.1 µg/m$^3$ based on an annual averaging time. The ITSL was established in 1991 and was based on the EPA's RfC from a 2-year rat inhalation study by Quast et al., 1980, which showed effects on nasal epithelium. The averaging time for the ITSL was originally set at the default of 24 hours, but is now being set at annual as supported by the key study and critical effect. The IRSL was established in 1987 and was based on the EPA's IRIS value from a study by Oberg et al., 1980.

Acrylonitrile (CAS# 107-31-1) is a colorless liquid which turns yellow in the presence of impurities with an onion- or garlic-like odor and a molecular weight of 53.06 g/mol. It is used: in the manufacture of plastics, such as polyacrylonitrile; in the manufacture of synthetic rubbers such as acrylonitrile butadiene; in the synthesis of certain polyamides; as a fumigant; and in the manufacture of acrylamide and acrylic acid. Acrylonitrile is highly flammable and toxic and can undergo explosive polymerization in the presence of heat, light, strong bases, strong acids, and strong oxidizers. When acrylonitrile burns it releases fumes of hydrogen cyanide and nitrogen oxides. The International Agency for Research on Cancer (IARC) has classified acrylonitrile as a Class 2B carcinogen (possible human carcinogen) and EPA has classified acrylonitrile as a probable human carcinogen (Group B1). Acrylonitrile is a possible human teratogen and a possible human developmental toxin. Acrylonitrile is found in auto exhaust, cigarette smoke, and industrial emissions (ATSDR, 2011; Sciencelab, 2013; Wikipedia, 2015).

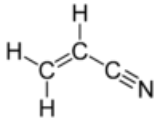


**Figure 1.** Structure of acrylonitrile.

**ITSL Derivation:**

The EPA RfC was used to derive the ITSL. EPA's RfC used a study by Quast et al., (1980) where "Sprague-Dawley rats (100/sex/concentration) were exposed 6 hours/day, 5 days/week for 2 years to concentrations of 0, 20, or 80 ppm acrylonitrile (duration-adjusted concentrations

of 7.7 and 31 mg/cu.m). The control group was exposed only to air. Additional animals were included for interim sacrifices at 6 months (n=7/sex/dose) and 12 months (n=13/sex/dose). A significant decrease in mean body weight was observed in the rats exposed to 80 ppm acrylonitrile. Less significant, but similar weight changes were noted in the 20-ppm females after approximately 1 month. A treatment-related effect on mean body weight was not observed in the 20-ppm males" (EPA, 1991).

"A statistically significant increase in mortality ($p<0.05$) was observed within the first year in both male and female rats administered 80 ppm and in the 20 ppm females during the last 10 weeks of the study. The apparent increase in reported mortality for the 20 ppm females was principally due to early sacrifice of rats with large, benign, mammary gland tumors (Quast, 1991). In Sprague-Dawley rats, these tumors occur spontaneously at a high rate, but in this experiment the tumors were observed earlier and more frequently, and became larger in exposed animals" (EPA, 1991).

"Exposure to acrylonitrile during the first 6-8 months resulted in a concentration-related increase in water consumption by both males and females. Urine specific gravity, which was repeatedly evaluated during this time interval, was usually decreased among rats exposed to 80 ppm. The authors noted increased pathologic changes to the heart and lungs of male rats of both groups, but indicated that they were identical to effects in the control rats that are usually associated with chronic renal disease. Microscopic analysis of the kidneys indicated a slight, nonstatistically significant increase in the incidence of spontaneously occurring advanced chronic renal disease. However, the slight increase could have been due to increased demand on the kidneys resulting from the increased water consumption seen earlier in the study" (EPA, 1991).

"Occasional significant deviation of the packed cell volume (PCV), and in the RBC, hemoglobin, and WBC counts were noted. However, the authors interpreted them as secondary changes associated with decreased growth, tumor formation, and hemorrhaging resulting from exposure to acrylonitrile. Urinalysis, hematology, and clinical chemistry were monitored. No other microscopic findings attributable to acrylonitrile exposure were observed. No adverse effects were observed on the bone marrow or liver function in rats in either sex exposed to 80 ppm" (EPA, 1991).

"Based on gross and histopathologic evaluation of tissues from over 40 different organs (including the respiratory tract and nasal turbinates), the two tissues which exhibited a treatment-related adverse effect due to acrylonitrile exposure were the nasal respiratory epithelium (4 transverse sections of the nasal turbinates were cut and examined) and the brain (9 sections through the CNS were cut and examined). Gross pathologic observations revealed significantly increased lung changes suggestive of pneumonia in 20 ppm male rats. Acute suppurative pneumonia was observed in the lungs of 10 male rats in the 80 ppm group between 7 and 12 months; it was occasionally observed in a single rat from the 20 ppm group. There were no indications of pneumonia in female rats of either exposure group. These changes are presumed to have been secondary effects related to the stress associated with the exposure" (EPA, 1991).

"A significant increase ($p<0.05$) in focal gliosis and perivascular cuffing was observed in the brains of high-concentration males (1/100 controls; 7/100 exposed) and females (0/100 controls; 8/100 exposed), but not in low-concentration rats. The incidence of glial cell tumors (astrocytomas) was significantly increased in the 80 ppm group over controls for both males (15/99 vs. 0/100 in controls) and females (16/100 vs. 0/100 in controls). The incidence of proliferative glial cell lesions suggestive of early tumors was significantly increased in the 80

ppm males (7/100 vs. 0/100 in controls), but not in the females at any level (4/100 at 80 ppm; 4/100 at 20 ppm; 0/100 in controls). Collectively, proliferative changes in the glial cells (i.e., tumors and early proliferation suggestive of tumors), were significantly increased in the 20 ppm (8/100) and 80 ppm (20/100) females over female controls (0/100), and in the 80 ppm males (22/99), but not in the 20 ppm males (4/99) when compared with male controls (0/100)" (EPA, 1991).

"There were significant degenerative and inflammatory changes ($p<0.05$; one-sided Fisher's Exact test) in the respiratory epithelium of the nasal turbinates at both exposure concentrations (20 and 80 ppm) which are interpreted to be treatment-related irritation of the nasal mucosa. In the male 20 ppm group, there was a slight but not statistically significant increase in the incidence of respiratory epithelium hyperplasia in the nasal turbinates (0/11 in controls; 4/12 at 20 ppm; 10/10 at 80 ppm) and a statistically significant increase in hyperplasia of the mucous secreting cells (0/11; 7/12; 8/10). In the 20 ppm females there was a slight but not statistically significant increase in focal inflammation in the nasal turbinates (2/11; 6/10; 7/10) and a statistically significant increase in flattening of the respiratory epithelium of the nasal turbinates (1/11; 7/10; 8/10). In the 80 ppm group, effects were more severe and were characterized by suppurative rhinitis, hyperplasia, focal erosions, and squamous metaplasia of the respiratory epithelium. No treatment-related effects in the olfactory epithelium, trachea, or lower respiratory system were observed in either males or females at either concentration. In this study, 20 ppm (HEC = 1.9 mg/cu.m) is considered a LOAEL for pathological alterations in the respiratory epithelium of the extrathoracic region of the respiratory system" (EPA, 1991).

EPA RfC derivation used the critical effects of degeneration and inflammation of nasal respiratory epithelium and hyperplasia of mucous secreting cells from the Quast et al., 1980 rat 2-year inhalation study. Since there were no NOAELs the LOAEL of 20 ppm was used in the derivation of the inhalation RfC. Conversion factors were determined using the molecular weight of acrylonitrile of 53.06, assuming 25°C and 760 mmHg.

$$LOAEL\ {}^{mg}/_{m^3} = \frac{20\ ppm\ \times 53.06}{24.45} = 43\ {}^{mg}/_{m^3}$$

$$LOAEL_{ADJ} = 43\ {}^{mg}/_{m^3}\ \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 7.7\ {}^{mg}/_{m^3}$$

"The $LOAEL_{HEC}$ was calculated for a gas:respiratory effect in the Extrathoracic region. MVa = 0.33 $m^3$/day, MVh = 20 $m^3$/day, $Sa_{ET}$ = 11.6 $cm^2$, $Sh_{ET}$ = 177 $cm^2$" (EPA, 1991).

$$RGDR_{ET} = \frac{(\frac{MV_a}{S_a})}{(\frac{MV_h}{S_h})} = \frac{(\frac{0.33\ {}^{m^3}/_{day}}{11.6 cm^2})}{(\frac{20\ {}^{m^3}/_{day}}{177 cm^2})} = 0.252$$

$$LOAEL_{HEC} = LOAEL_{ADJ} \times RGDR = 7.7\ {}^{mg}/_{m^3}\ \times 0.252 = 1.9\ {}^{mg}/_{m^3}$$

"The uncertainty factor of 1000 reflects a factor of 10 to protect unusually sensitive individuals and 3 to adjust from a minimally adverse LOAEL to a NOAEL. An uncertainty factor of 3 for interspecies variability is used because the use of the dosimetric adjustments account for part of this area of uncertainty. An additional factor of 10 is applied due to an incomplete database, or more specifically, the lack of an inhalation bioassay in a second species, and the lack of reproductive data by the inhalation route with the existence of an oral study showing reproductive effects" (EPA, 1991). This gives an RfC of 2E-3 mg/$m^3$.

Rule 232(1)(a) states that a RfC can be used as an ITSL, therefore the ITSL for acrylonitrile is 2 µg/$m^3$. Rule 232(2)(b) states that the default averaging time is 24-hours, however in this case the critical effect and study duration support an annual averaging time as allowed under Rule 229(2)(b).

**IRSL Derivation:**

EPA has determined that acrylonitrile is a Class B1 (probable human carcinogen) based on "the observation of a statistically significant increase in incidence of lung cancer in exposed workers and observation of tumors, generally astrocytomas in the brain, in studies in two rat strains exposed by various routes (drinking water, gavage, and inhalation) forms the basis for this classification" (EPA, 1991).

EPA derived a quantitative estimate of carcinogenic risk from inhalation exposure with an inhalation unit risk of 6.8x$10^{-5}$ per µg/$m^3$ using dose-response data from a study by O'Berg (1980) showing increased respiratory cancer in humans, "O'Berg (1980) observed 25 cases of cancer, including eight cases of respiratory cancer, in 1345 male textile workers exposed to acrylonitrile and followed for 10 or more years. Estimated levels of exposure were 5-20 ppm acrylonitrile. All of the cancer cases, except for one nonrespiratory cancer, occurred among 1128 workers with 6 or more months exposure (SIR=126, SMR=113). A trend of increased cancer incidence was seen with increased duration of exposure and increased length of follow-up time. The excess of respiratory cancer was statistically significant and remained so upon evaluation of the contribution of smoking (five observed vs. 1.6 expected)" (EPA, 1991).

A study that supports the human data comes from the Quast et al., (1980) study where Sprague-Dawley rats (100/sex/group) were administered acrylonitrile via inhalation at 0, 20, and 80 ppm for 6 hours/day, 5 days/week for 2 years. This study found a statistically significant increase of tumors in the CNS and other sites (see above for full study description).

The unit risk was calculated from a relative risk model adjusted for smoking and based on continuous lifetime equivalent of occupational exposure

$$Unit\ Risk = \frac{PO(R-1)}{X} = (1.5E-4)/ppb \times \frac{\frac{0.45}{ppb}}{\frac{\mu g}{m^3}} = 6.8E-5\ (\mu g/m^3)^{-1}$$

"Where: PO = 0.036 = background lifetime probability of death from respiratory cancer
R = 5.0/1.6 = 3.1 = relative risk of respiratory cancer adjusted for smoking (O'Berg, 1980).

X = 500 ppb = continuous equivalent lifetime exposure when 9 years = estimated average exposure duration, and 60 years = estimated maximum possible age at end of observation period" (EPA, 1991).

"The excess incidence of respiratory cancer in the O'Berg (1980) study was adjusted for smoking. An exposure of 15 ppm was assumed to be the 8-hour TWA with an average exposure duration of 9 years. The maximum possible age at the end of the observation period was assumed to be 60 years" (EPA, 1991).

The calculated inhalation unit risk is $6.8 \times 10^{-5}$. Rule 231(1) was used to develop the IRSL, using the inhalation unit risk value derived by EPA for acrylonitrile. The equation is below:

$$IRSL = \frac{1 \times 10^{-6}}{Unit\ Risk} = \frac{1 \times 10^{-6}}{6.8 \times 10^{-5}} = 0.014705882\ {}^{\mu g}/_{m^3}$$

Rule 231(4) states that the averaging time for IRSLs and SRSLs is an annual averaging time. The initial risk screening level (IRSL) for acrylonitrile (CAS# 107-13-1) is 0.01 µg/m$^3$ and the SRSL is 0.1 µg/m$^3$ based on an annual averaging time.

**References:**


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