

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: Ethyl acrylate file (CAS # 140-88-5)

FROM: Gary Butterfield

SUBJECT: Screening level for Ethyl acrylate

DATE: July 22, 2008

In the late 1980s, the AQD established a cancer potency of 1.4×10^{-5} ($\mu\text{g}/\text{m}^3$)⁻¹ with the associated 1 in one million risk value of $0.07 \mu\text{g}/\text{m}^3$ for ethyl acrylate based on a two-year oral gavage NTP bioassay (NTP 1986). This inhalation potency has a corresponding oral potency value of $0.048 (\text{mg}/\text{kg})^{-1}$, which is similar to the oral potency developed by the EPA as was listed in the 1997 Health Effects Assessment Summary Tables (HEAST). The AQD recently received a request from the Basic Acrylic Monomer Manufacturers, Inc. (BAMM) to reassess the existing screening level. BAMM submitted information to the AQD, which they felt indicated that ethyl acrylate does not present a carcinogenic hazard to humans. The purpose of this current evaluation is to review the information submitted by BAMM, update and evaluate the literature, and determine if it is appropriate to change the existing screening level that was set in the 1980s.

Ethyl acrylate is also known as EA, the ethyl ester of acrylic acid, or 2-propenoic acid ethyl ester. Ethyl acrylate is a clear liquid with an acrid penetrating odor. The molecular formula is $\text{C}_5\text{H}_6\text{O}_2$. The molecular weight is 100.1 g/mol. The boiling point of ethyl acrylate is 99C. The melting point is -71C. The vapor pressure at 25C is 38.6 mmHg. The odor threshold is reported to be 1.2 ppb or $4.9 \mu\text{g}/\text{m}^3$. Major uses for ethyl acrylate include chemical intermediate in the formation of esters for polymer manufacture for use in paints, paper, and fabrics. Ethyl acrylate is a highly reactive air contaminant, and can be expected to cause toxic effects early in the respiratory tract; i.e., in the nasal cavity, when inhaled.

Ethyl acrylate is one of the EPA's 187 HAP chemicals. It was included by the EPA in the 1999 National Air Toxics Assessment (NATA). NATA's evaluation considered ethyl acrylate to be a carcinogen, and used the HEAST oral potency adjusted to an inhalation potency (matching the 1980s AQD), as the EPA doesn't have any IRIS values.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH) Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), Michigan Department of Environmental Quality (DEQ) library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1968 - June 2008), National Library of Medicine (NLM) - Toxline, and National Toxicology Program (NTP) Status Report.

The CAS and NLM on-line literature searches for this evaluation were conducted on June 17, 2008. There is an ACGIH TLV of 5 ppm (or 20 mg/m³) for ethyl acrylate. Note that this TLV is three orders of magnitude greater than the odor threshold. The 2001 TLV documentation says that this exposure concentration will minimize irritation effects on the respiratory tract and mucus membranes, and may help prevent sensitization responses. The documentation identifies some adverse effects; drowsiness, headaches, and nausea, that occurred in humans with prolonged exposures of 50 to 70 ppm (or 205 to 286 mg/m³).

It should be noted that the odor threshold for ethyl acrylate has been reported to be in the range of 0.5 to 1.2 ppb or 2 to 5 ug/m³. The ethyl acrylate odor is considered to be quite offensive. Unfortunately, the available human exposure to ethyl acrylate data is not of adequate quality to provide the basis of setting a screening level. The human data is considered to be anecdotal, either describing accidental exposures to unknown high concentrations, exposures to relatively high concentrations that did show adverse effects, or exposure to low doses that were conducted for finding an odor threshold. None of these types of studies are adequate for setting a screening level.

NTP (1986) reports the results of carcinogenesis studies of ethyl acrylate that were conducted by administering of this test chemical in corn oil by gavage to groups of 50 male and 50 female F344/N rats and B6C3F1 mice at doses of 0, 100 or 200 mg/kg. Ethyl acrylate was administered five times per week for 103 weeks. Groups of 50 rats and 50 mice of each sex received corn oil by gavage on the same schedule and served as vehicle controls. There was a compound-related increased incidences of hyperkeratosis, inflammation, and hyperplasia of the forestomach observed in rats and mice in the prechronic, as well as 2-year studies. In the 2-year studies, squamous cell papillomas and squamous cell carcinomas of the forestomach occurred at the site of chemical deposition with significant positive trends and increased incidences in dosed groups versus vehicle controls for both sexes of rats and mice. Nonneoplastic and neoplastic forestomach lesion frequencies were related to the concentration of ethyl acrylate in dosing solutions used. Significant negative trends for several common rodent tumors were found in treated animals in the 2-year studies. Under the conditions of these studies, ethyl acrylate was found to be carcinogenic for the forestomach of F344/N rats and B6C3F1 mice, causing squamous cell carcinomas in male rats and male mice, squamous cell papillomas in male and female rats and male mice, and squamous cell papillomas or carcinomas (combined) in male and female rats and mice. Evidence for carcinogenicity was greater in males than in females. Ethyl acrylate also caused irritation of the forestomach mucosa in male and female rats and mice.

Although the positive NTP gavage study was the basis for ethyl acrylate being listed on the old NTP and IARC list of carcinogenic chemicals, NTP has in recent years determined that the high dose gavage study is not relevant to human risk assessment as humans are usually exposed to ethyl acrylate via inhalation or dermal exposures. IARC has not conducted a re-evaluation of ethyl acrylate carcinogenic classification as of this time. However, BAMM indicates that they have requested IARC conduct a re-evaluation, and that may occur in the next year or two - depending on IARC scheduling constrains. The EPA web-pages do not have any indication of recent EPA decisions to classify ethyl acrylate as a non-carcinogen. The newer web-pages do cite NTP's decision to delist from ROC, but EPA has not recently had an official decision to remove the old B2 classification for ethyl acrylate.

NTP 2000 in the 9th ROC delisted ethyl acrylate from the list of carcinogens. The documentation of the delisting as found in the 2005 11th Report on Carcinogens states, "...it was found that the majority opinion of the Report on Carcinogens review groups was to recommend that

ethyl acrylate be removed from the Report on Carcinogens. This was based on the facts that 1) the forestomach tumors induced in animal studies were seen only when ethyl acrylate was administered by gavage at high concentrations that induced marked local irritation and cellular proliferation, 2) animal studies by other routes of administration including inhalation were negative, and 3) because significant chronic human oral exposure to high concentrations of ethyl acrylate monomer is unlikely. Therefore ethyl acrylate does not meet the criteria to be listed in the Report on Carcinogens as reasonably anticipated to be a human carcinogen.”

Among the few epidemiology studies, Walker et al. (1991) evaluated the mortality from cancer of the colon or rectum among workers exposed to EA and methyl methacrylate (MMA). This study was summarized in the 1998 NTP background document as follows.

“Three cohorts were assembled consisting of white male workers associated with acrylic sheet manufacturing facilities at Bristol, Pennsylvania (employed between 1933 and 1945); later at Bristol (hired between 1946 and 1982); and at Knoxville, Tennessee (employed between 1943 and 1982). All cohort members were traced until death or December 1986. The split in the Bristol cohort was due to changes in production methods. Following an explosion in 1943 at the EA production facility, the proportion of EA in the polymerization mixture was changed immediately from 12 to 6%, with a subsequent decline to zero in the following decade. However, EA was used elsewhere in the same buildings in which acrylic sheet was produced, even after its use in acrylic sheet production was discontinued completely. The two cohorts (later Bristol and Knoxville), with later dates of hire, showed no excess mortality from any cause, including colon cancer or rectal cancer. In the earliest Bristol cohort, excess colon cancer seemed restricted to men employed extensively in the early 1940s in jobs entailing the highest exposures to vapor-phase EA and MMA monomer, and volatile by-products of the EA/MMA polymerization process. The excess mortality appeared 20 years after the equivalent of three years work in jobs with the most intense exposures. A smaller elevation in colon cancer mortality appeared in a low-exposure group in the early Bristol cohort. Rectal cancer mortality was elevated in the same categories that showed excess rates of colon cancer death; however, due to lower rates, the rectal cancer results are less precise. The EA/MMA exposures of members of the three cohorts were estimated on the basis of job histories and job-specific exposure rating scales. Monitoring data for EA/MMA were available only from the Bristol plant beginning in 1972; earlier levels of exposure to EA/MMA were reconstructed from production records and interviews with plant personnel. The resulting exposure scales were semiquantitative, pertained to vapor exposure only, did not distinguish between EA and MMA, relied on the recollection of long-term employees, were not verifiable, were not mutually comparable across all three cohorts, and did not take into account the presence of other substances in the workplace. These other substances included some which have subsequently been considered as either probable or possible carcinogens by the IARC (lead, ethylene dichloride, methylene chloride, and acrylonitrile) (Walker et al. 1991).”

The NTP 1998 background document also evaluated the possible mutagenic effects of ethyl acrylate with the following summary. “The genotoxicity of ethyl acrylate (EA) has been investigated extensively in both in vitro and in vivo assays. The in vitro assays demonstrate that EA can induce DNA damage including chromosomal aberrations and gene/point mutations. When tested in vivo, EA was found to be nonmutagenic in systems measuring both the induction of chromosomal damage and induction of gene/point mutations. The lack of mutagenicity in vivo is consistent with data in rats on its rapid metabolism by hydrolysis to

acrylic acid (IARC 1986). Thus, EA has mutagenic potential for the induction of chromosomal damage that is not fulfilled in vivo due to its rapid metabolism. In conclusion, the in vitro and in vivo data on the genotoxicity of EA are consistent with the interpretation that EA should be considered non-genotoxic to exposed human populations.”

The NTP decision to classify the carcinogenicity of ethyl acrylate as not a likely human carcinogen is supported by the available non-genotoxic evidence following ethyl acrylate exposure in whole animals, and the lack of cancer findings from epidemiology studies. This has led to the AQD deciding to also consider ethyl acrylate to be non-carcinogenic and remove the IRSL/SRSL from the screening level list. The available non-carcinogenic studies were then evaluated for ITSL development.

There has been a few inhalation developmental toxicity studies conducted with ethyl acrylate. Saillenfait et al (1999) is a good example of these studies. Sprague-Dawley rats were exposed 6 hours a day on gestation days 6 to 20 to concentrations of 25, 50, 100, or 200 ppm ethyl acrylate. There were no increases in treatment related embryo/fetal mortality, or fetal malformations from exposure to ethyl acrylate. Fetal toxicity was observed as decreased fetal body weight at 200 ppm. However maternal toxicity was also observed to occur at 200 ppm – decreased body weight gain. These developmental study exposure levels are relatively high compared to available chronic duration studies, which found respiratory tract changes at much lower concentrations than those where the maternal or fetal toxicity occurred. Therefore, use of the chronic duration inhalation study as the basis to set the screening level will be protective of development of potential fetal health effects from exposure to ethyl acrylate.

The lifetime rat and mouse inhalation study conducted by Miller et al (1985), which exposed groups of 60 to 90 animals/sex of F344 rats and B6C3F1 mice for 6 hours a day, 5 days a week for up to 27 months to concentrations of 0, 5, 25, 75 or 225 ppm. The main exposure related adverse effect observed in this study was nasal tissue histopathology changes occurring at 25 ppm and higher doses. There was a concentration-dependent increase in severity and distribution of nasal mucosa olfactory epithelium lesions in rats and mice. The authors reported there were no adverse effects observed in the groups exposed to 5 ppm, making 5 ppm the NOAEL from this study.

There are available other chronic studies that have been conducted with ethyl acrylate by the oral and dermal routes of exposure. Those studies also did not find any evidence of carcinogenic effects. However, for the purpose of setting a screening level, the NOAEL of 5 ppm for nasal tissue histopathology changes from the chronic inhalation exposure study by Miller et al (1985) provides the best basis for setting an ITSL. One method of calculating a screening level, utilizing the new BMD methodology, was conducted. The Miller et al article did not give any details on the 5 ppm group. It was reported that no nasal pathology was observed in the 5 ppm dose group, so it was assumed that there were zero cases in the group of 90 when entering the incidence rates in to the BMD models. It should also be noted that the BMD models gave the best fit when the two highest dose levels were omitted. There is some concern with using the BMD models to analyze results from a study where complete incidence rates for one dose level were not given, and 2 of 5 doses are dropped from model inclusion. These are indications that BMD methodology should not be used for derivation of the ethyl acrylate screening level. Therefore, the ITSL will be calculated using the EPA RfC NOAEL/LOAEL methodology as follows. The questions arose as to which species, rats or mice, would have the smaller ITSL from this study, so possible screening levels were calculated for each species.

For rats:

$$\text{NOAEL} = 5 \text{ ppm} = 20.5 \text{ mg/m}^3$$

$$\text{NOAEL}_{(\text{ADJ})} = 20.5 \text{ mg/m}^3 \times 6/24 \times 5/7 = 3.65 \text{ mg/m}^3$$

Ethyl acrylate can be considered to be a Category 1 gas, with extra-thoracic effects (nasal tissues changes). The RGDR calculated based on the ratio of (ventilation rate)/(extra thoracic surface area) for rats over humans.

$$\text{RGDR} = \frac{(v_a/\text{SA}_a)}{(v_h/\text{SA}_h)} = \frac{((.29\text{L}/\text{min})/(15\text{cm}^2))}{((13.8\text{L}/\text{min})/(200\text{cm}^2))} = 0.281$$

$$\text{NOAEL}_{(\text{HEC})} = 3.65 \text{ mg/m}^3 \times 0.281 = 1.02 \text{ mg/m}^3$$

$$\text{RfC} = (1.02 \text{ mg/m}^3)/(10 \times 3) = 34 \text{ ug/m}^3 \text{ rounded to } 30 \text{ ug/m}^3 \text{ with 24 hour average}$$

The uncertainty factor of 10 for sensitive individuals, and a factor of 3 for animal-to-human were used in the above RfC calculation. The animal-to-human factor is reduced from 10 to 3 because use of the RGDR compensates for a portion of the 10 fold factor.

For mice:

$$\text{NOAEL} = 5 \text{ ppm} = 20.5 \text{ mg/m}^3$$

$$\text{NOAEL}_{(\text{ADJ})} = 20.5 \text{ mg/m}^3 \times 6/24 \times 5/7 = 3.65 \text{ mg/m}^3$$

Ethyl acrylate can be considered to be a Category 1 gas, with extra-thoracic effects (nasal tissues changes). The RGDR calculated based on the ratio of (ventilation rate)/(extra thoracic surface area) for mice over humans.

$$\text{RGDR} = \frac{(v_a/\text{SA}_a)}{(v_h/\text{SA}_h)} = \frac{((.0435\text{L}/\text{min})/(3\text{cm}^2))}{((13.8\text{L}/\text{min})/(200\text{cm}^2))} = 0.21$$

$$\text{NOAEL}_{(\text{HEC})} = 3.65 \text{ mg/m}^3 \times 0.21 = 0.767 \text{ mg/m}^3$$

$$\text{RfC} = (0.767 \text{ mg/m}^3)/(10 \times 3) = 26 \text{ ug/m}^3 \text{ rounded to } 30 \text{ ug/m}^3 \text{ with 24 hour average}$$

The uncertainty factor of 10 for sensitive individuals, and a factor of 3 for animal-to-human were used in the above RfC calculation. The animal-to-human factor is reduced from 10 to 3 because use of the RGDR compensates for a portion of the 10 fold factor.

A comparison of the rat versus the mouse based ITSL shows very little difference. When rounded to a single significant figure there is no difference in the ITSL values. Therefore, the ITSL for ethyl acrylate is being established at 30 ug/m³ with 24 hour averaging, following the calculated RfC based on the Miller et al (1985) NOAEL.

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