**MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY**

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**INTEROFFICE COMMUNICATION**

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TO: Amyl Acetate Mixture

FROM: Mike Depa, Air Quality Division, Toxics Unit

SUBJECT: ITSL Change in the Averaging Time from 24 Hours to Annual

DATE: April 22, 2016

The current Initial Threshold Screening Level (ITSL) for amyl acetate mixture is 1100 µg/m$^3$ and has a justification (attached) dated March 8, 1999. 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**

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**INTEROFFICE COMMUNICATION**

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March 8, 1999

TO: Amyl acetate (mixture) file

FROM: Gary Butterfield. Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level (ITSL) for amyl acetate

Amyl acetate is sometimes called primary amyl acetate or n-amyl acetate. The commercially available product is a mixture consisting of 65% n-amyl acetate (CAS #628-63-7) and 35% 2-methyl butyl acetate (CAS # 624-41-9). This industrial mixture of n-amyl acetate does not have a specific CAS number and frequently goes by the 628-63-7 CAS number.

The occupational exposure levels (OELs) for several individual amyl acetates (n-amyl acetate, sec-amyl acetate and iso-amyl acetate) are available from ACGIH and NIOSH. These 8 hour time-weighted average (TWA) OELs are of the order of 100 ppm or 532 $mg/m^3$. These OELs have documentation that essentially treats all amyl acetates as having similar toxic effects. If these OELs were used to determine the ITSL a screening levels of 5320 $\mu g/m^3$ with 8 hour averaging would occur. However, the OEL documentation does indicate that the toxicity basis for these OELs is not very good. With some of the OELs set for guarding against irritation with very little data to base the selection of the OEL. If here is a general lack of toxicity data for individual amyl acetate compounds.

There is also a similarity in toxicity of these various amyl acetate compounds, as evidenced by the OELs covering all isomers and a similarity of LD5O values for the individual amyl acetate compounds (see the appendix). At this time, it will be considered appropriate to develop an ITSL for the industrial amyl acetate mixture (consisting of 65% n-amyl acetate and 35% 2-methyl butyl acetate) and then apply that screening level to each of the individual amyl acetate compounds, rather than basing the ITSL on the default value.

On August 27,1998, a CAS and NLM on-line literature searches were conducted to see if any new articles were available since the literature search for amyl acetate was conducted in July 1997. In 1997, almost no toxicity data was discovered during that review. Very limited amounts of toxicity studies have been published in peer reviewed journal articles for amyl acetate. No new information that was relevant for calculation of

a screening level was identified in the 1998 CAS search. However, the 1998 NLM on-line search identified a few unpublished studies including, a subchronic toxicity study, a couple of developmental toxicity studies, and a few acute studies that have been submitted to EPA under ToSCA section 8(e). The subchronic study and developmental studies may provide a better toxicological basis for a screening level as calculated by EPA's RfC methods, rather than basing a screening level on the relatively poorly documented OELs. One of the studies submitted to EPA's ToSCA program was a rat 13 week inhalation study which was reported by Bio-Research Laboratories (1997). In this study, rats were exposed to 'n-amyl acetate' which was actually the commercial mixture of 65% n-amyl acetate and 35% 2-methyl butyl acetate. Sprague-Dawley rats, ten of each sex per dose level, were exposed for 6 hours a day, 5 days a week to levels of 0, 299, 600 or 1199 ppm. This study identified 1199 ppm as the no effect level. No effects occurred at any dose levels tested in this study. Following the EPA RfC methodology the ITSL can be calculated as follows.

NOAEL(adj) 1199 ppm x (5.32 mg/m$^3$ /ppm) x 6/24 x 5/7 = 1140 mg/m$^3$
NOAEL(hec) = NOAEL(adj) because there is no information to indicate that rats are different than humans
ITSL = RfC = 1140 mg/m$^3$/(10x10x10) = 1100 µg/m$^3$ with 24 hour averaging

Where an uncertainty factor of 10 was used for each of the following: sensitive individuals within the population; inter-species conversion; and subchronic to chronic adjustment. In addition to the above 13 week study, there was a couple of unpublished developmental toxicity studies reported to EPA. In one of the developmental toxicity studies, groups of 25 pregnant F344 rats were exposed for 6 hours a day to primary amyl acetate, which also is the commercial mixture of 65% n-amyl acetate and 35% 2-methyl butyl acetate, at concentrations of 0, 500, 1000 or 1500 ppm during gestation days 6 to 15 BRRC (1994a). Maternal toxicity was evident as decreased weight gain in the 1500 ppm exposure level. Thus the 1000 ppm was identified as the maternal NOAEL. The fetal NOAEL was identified as 500 ppm in this study. There was a decrease in the female fetal body weights at both 1000 and 1500 ppm. In a second developmental toxicity study, groups of 15 pregnant New Zealand rabbits were exposed for 6 hours a day to the primary amyl acetate mixture at the same concentrations of 0, 500, 1000 or 1500 ppm during gestation days 6 to 18 BRRC (1994b). Maternal toxicity, body weight loss and decreased food consumption, was observed at 1500 ppm. The maternal NOAEL was 1000 ppm. In this study there was no effects on the fetuses at any dose level. Thus the fetal NOAEL was 1500 ppm. Although a couple of developmental studies have been conducted, for the purposes of calculating an RfC, amyl acetate can be considered to be insufficiently tested for reproductive effects because a multigenerational study has not yet been conducted. Based on the available information, the developmental RfC can be calculated as follows. The NOAEL of 500 ppm was selected in order to protect fetuses of the more sensitive tested species, rat. This NOAEL was selected by assuming that humans are just as sensitive as rats. Therefore, the NOAEL of 500 ppm will be used in these calculations.

NOAEL(adj) = 500 ppm x (5.32 mg/m³ /ppm) x 6/24 = 665 mg/m³
NOAEL(hec) = NOAEL(adj) because there is no info to indicate rats are different than Humans

RfC(dt) = 665 mg/m³/(10x10) = 6500 µg/m³ with 24 hour
Where an uncertainty factor of 10 was used for each of the following: sensitive individuals within the population; and inter-species conversion.

The calculated RfC(dt) of 6500 µg/m³ is greater than the RfC(dt) 1100 µg/m³ which was based on the subchronic effects NOAEL. Therefore the use of the RfC of 1100 µg/m³ as the screening level should be sufficient to protect fetuses from developmental effects. The ITSL of 1100 µg/m³ with 24 hour averaging is being adopted for the amyl acetate isomer mixture by AQD at this time.

**References:**

Bio-Research Laboratories 1997 A 13 week inhalation neurotoxicity study by whole body exposure of n-amyl acetate vapor in the albino rat. EPA OTS # 0558895.

BRRC 1994a. Developmental toxicity study of primary amyl acetate vapor in F344 rats. EPA doc #8EHQ-0294-1263 OTS #0529947-1.

BRRC 1994b. Developmental toxicity study of primary amyl acetate vapor in New Zealand white rabbits. EPA doc #8EHQ-0294-l263 OTS #0529947-1.

Attachment

Appendix A: Comparison of various amyl acetate's toxicity

The following table lists the CAS numbers, chemical name and synonyms of amyl acetates, the OEL, and the LD50 if it is known. The similarity of the level of the few amyl acetate LD50's is also an indication that it may be likely to handle these compounds as having similar toxic effects. In the bottom half of this table is a listing of possible alcohol products which would be produced from disassociation of these acetate esters. The amyl acetates are expected to hydrolyze to alcohol and acetic acid as the first metabolic step. The OEL's and oral LD50's from RTECS for those alcohols are also listed. All of these 5-carbon alcohols have relatively low acutely toxicity, with LD50's in the 1 to 3 g/kg range

| CAS # | Chemical | OEL | Oral LD50 | Reference |
|---|---|---|---|---|
| | | | | |
| 628-63-7 | n-pentyl acetate | TLV=100 ppm (532 mg/m3) | rbt 7.4 g/kg | Czech (1986) |
| | n-amyl acetate | | | |
| | | | | |
| 123-92-2 | iso-amyl acetate | TLV=100 ppm (532 mg/m3) | rat 16.6 g/kg | Japan (1981) |
| | 3-methyl butyl acetate | | rbt 7.4 g/kg | Ind Med surgy 41:31 (1972) |
| | | | | |
| 626-38-0 | sec-amyl acetate | TLV=125 ppm (665 mg/m3) | | |
| | 1-methyl butyl acetate | | | |
| | | | | |
| 624-41-9 | 2-methyl butyl acetate | | | |
| | | | | |
| | | | | |
| Some alcohols which may metabolically come from the above esters - summary of LD50's from RTECS | | | | |
| | | | | |
| CAS # | Chemical | OEL | Oral LD50 | reference |
| | | | | |
| 75-85-4 | 2-methyl-2-butanol | 100 ppm (360 mg/m3) | rat 1 g/kg | Science 116:663 (1952) |
| | tert-pentanol | | rbt 2 g/kg | Ind Med Surgy 41:31 (1972) |
| | | | | |
| 71-41-0 | 1-pentanol | 100 ppm (360 mg/m3) | rat 2.2 g/kg | Russian 1976 |
| | n-amyl alcohol | | mus 200 mg/kg | Russian 1970 |
| | | | | |
| 123-51-3 | 3-methyl butanol | PEL=100 ppm (360 mg/m3) | rat 1.3 g/kg | S African Med J 43:795 (1969) |
| | iso-amyl alcohol | TLV= 100 ppm (360 mg/m3) | rbt 3.4 g/kg | Ind Med Surgy 41:31 (1972) |
| | | | | |
| 137-32-6 | 2-methyl butanol | | rat 1 g/kg | Science 116:663 (1952) |
| | | | | |
| 6032-29-7 | sec-amyl alcohol | PEL = 100 ppm (360 mg/m3) | rbt 2.8 g/kg | Ind Med Surgy 41:31 (1972) |
| | 2-pentanol | | | |