MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Formic Acid (CAS # 64-18-6)

FROM: Robert Sills, AQD Toxics Unit Supervisor

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

DATE: December 29, 2015

The current ITSL for Formic Acid (2 ug/m^3) was derived on May 15, 2008 (see attached justification memo). The averaging time (AT) assigned to the ITSL at that time was 24 hours, as per the default methodology at that time (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 NATURAL RESOURCES

INTEROFFICE COMMUNICATION

February 23, 1995

TO: File for Formic Acid (CAS # 64-18-6)

FROM: Dan O'Brien

SUBJECT: Initial Threshold Screening Level for Formic Acid

The initial threshold screening level (ITSL) for Formic Acid (CAS # 64-18-6) is 2 $\mu g/m^3$ based on a 24 hour averaging time.

The following references or databases were searched to identify data to determine the ITSL and IRSL: AQD chemical files, IRIS, HEAST, ACGIH TLV Booklet, NIOSH Pocket Guide to Chemical Hazards, RTECS, NTP Management Status Report, EPB Library, IARC Monographs, CAS On-line and NLM/Toxline (1967 -June 7, 1994).

Formic acid occurs widely in nature in a variety of plants, foods, and as a constituent of insect venoms. It is used extensively in industrial applications as a decalcifier, in textile dyeing and finishing, and in the tanning of leather (NTP, 1992). It is also employed as a fungistat, a plasticizer for vinyl resins, a latex coagulator, and in the manufacture of perfumes, flavors, drugs, insecticides and refrigerants.

The compound is caustic, and much of the toxicity information available in the literature relates the clinical toxicology associated with accidental ingestion by children (von Muhlendahl, *et al.*, 1978), intentional ingestion by adults, and with accidental industrial exposures (von Oettingen, 1959). Consistent with its corrosive nature, most of the reported clinical signs in humans involve severe irritation of exposed tissues, with inflammation and systemic shock as sequelae. Humans are also exposed to formic acid as an intermediate in methanol poisoning (Liesivuori and Savolainen, 1991), and as a component of vegetation smoke (Dost, 1991). Because exposures in these reports were either poorly characterized or at a level where frank effects were elicited, they are not useful for the quantitative derivation of a screening level.

Some epidemiological studies concerning possible effects of occupational exposure to formic acid have been carried out by Finnish investigators (Liesivuori and Kettunen, 1983; Liesivuori *et al.*, 1992). In Nordic countries, formic acid is applied to harvested forage crops to make silage. Consequently, farmers are the "at risk" group. These studies concentrated methodologically on exposure assessment, but as a result, potential health effects were not studied in a rigorous manner. Liesivuori and Kettunen (1983), in a preliminary report, noted breathing zone air concentrations of 0-99 mg/m^3, depending on the individual silage-making task; the highest exposures were measured as the silage was top-dressed with formic acid in the silo. Mean breathing zone air concentrations during that task reached 87 mg/m^3. The only health effect reported was "typical asthma-like dyspnea" in one asthmatic. The small cohort study of Liesivuori *et al.* (1992) calculated a eight hour TWA exposure in a cohort of twelve farmers to

be 7.3 ± 2.2 mg/m^3 (mean ± S.D.), based on breathing zone air samples. A strong linear relationship was noted between formic acid concentrations in air and those in the farmers' urine, both above and below the Finnish hygienic limit of 9 mg/m^3. Urine formic acid concentrations were highly significantly greater in farmers than controls at 30 hrs. post-exposure. The implication of these high urine concentrations, according to the authors, was that formic acid could "potentially exert negative effects on health through impaired calcium reabsorption in the kidney" by impeding ATP production at the mitochondrial level. They further suggested that the hygienic limit of 9 mg/m^3 would be associated with adverse renal biochemical effects, and so was not protective. While these studies offer supportive evidence of potential human effects due to low-level formic acid exposure, neither was adequate for use in the derivation of a screening level.

Although ACGIH (1991) has established a TWA Threshold Limit Value (TLV) of 9.4 mg/m^3 and a Short-Term Exposure Limit (STEL) of 19 mg/m^3 for formic acid, examination of the TLV documentation shows that the TLV appears to be based on a citation from Patty's Industrial Hygiene and Toxicology (Fassett, 1963), wherein the author suggests a limit of 5-10 ppm but provides no health-based rationale or justification. In light of this insufficient documentation, setting a screening level based on this occupational exposure limit (per Rule 232(1)(c) of Act 348) may be inappropriate.

The carcinogenicity of formic acid has been under review by an EPA workgroup since 9/5/91 (IRIS, 1994). It was not possible at the time of this writing to gain access to a review draft of a carcinogenicity assessment. The Ames/*Salmonella* mutagenicity assay was negative both with and without liver S9 metabolic activation, as tested by NTP (1992). Mutagenicity tests on *Salmonella typhimurium* were also negative both in the presence and absence of liver S9 activation in both Sprague-Dawley rats and Syrian golden hamsters (Zeiger *et al*, 1992). Sipi *et al* (1992), using sister chromatid exchanges in cultured human lymphocytes as an endpoint, found a 48 hr exposure to formic acid to induce slightly but significantly ($p < 0.01$) more sister chromatid exchanges than control, but only at the highest tested concentration (10 mM), not at the two lower concentrations (2.5 and 5.0 mM). These authors characterized this weakly positive response to formic acid as slightly mutagenic, and felt that this response could only be partially attributed to a lowering of the medium pH by the test chemical.

Subchronic inhalation toxicity studies of formic acid have been conducted in F344/N rats and B6C3F$_1$ mice by the National Toxicology Program (NTP, 1992), and as these are the most recent, highest quality data identified in the literature searches, they constitute the key study to be used in the derivation of the screening level. Groups of 10 animals of each sex and species were exposed to formic acid vapor by whole body exposure at target concentrations of 0, 8, 16, 32, 64 and 128 ppm for 6.5 hrs per day, five days per week for 13 wks. Ten additional rats were included for clinical pathology at days 3 and 23 of the study. The animals were observed daily for clinical signs, and body weights measured at the start and end of the study, and weekly in between. Other studied parameters included organ weights, hematology, clinical chemistry, urinalysis, and in the 0, 8, 32 and 128 ppm groups, sperm morphology/motility/density and vaginal cytology. All animals were subjected to necropsy and histopathology at the time of death or at termination; a complete collection of body tissues was obtained from all control and high-dose individuals. Respiratory tracts were obtained from rats in the other dose groups, and nasal sections from mice in the other dose groups. All gross lesions in all animals were examined histologically.

There was no mortality in the rats, nor were any exposure-related clinical signs noted. Male rats in the 32 ppm dose group experienced mild but significantly increased body weights relative to controls, and body weight gains were significantly greater than controls in the 16, 32 and 64 ppm males. Changes in

hematological and chemistry tests were minimal to mild in severity, and while some were statistically significant, in general they did not show consistent temporal, sex or dose relationships. No unusual gross lesions were noted. Absolute liver weights were significantly increased in all exposed males, and relative liver weights significantly increased in the 32, 64 and 128 ppm males. Both absolute and relative lung weights were decreased significantly in all exposed females and in the two highest exposure groups among the males; relative lung weights were decreased in the three lowest male exposure groups as well. Histopathologic changes in rats attributable to exposure were limited to the nose and generally to the highest exposure level. Squamous metaplasia of the nasal respiratory epithelium was present in 9 of 10 males and 6 of 10 females in the 128 ppm group; it was considered to be of minimal severity. Olfactory epithelial degeneration was found in 9 of 10 males and 5 of 10 females at the 128 ppm level; one male each in the 32 and 64 ppm groups also exhibited this lesion. All of the nasal olfactory epithelial lesions were considered to be minimal to mild in severity. There were no exposure related effects on any reproductive indices studied.

In mice, one animal of each sex died prior to termination. Both were in the 128 ppm exposure group. There were no exposure-related clinical signs. Compared to controls, body weight gains were significantly decreased in both sexes at 128 ppm and in males at 64 ppm. As a consequence, relative weights of most organs (heart, liver and kidney in both sexes, testis in males and lung in females) were increased relative to controls in the high dose group. There were no other consistent changes. There were no exposure-related gross lesions in mice; the only histological lesion attributable to formic acid exposure was minimal nasal olfactory epithelial degeneration. This lesion affected 2 of 10 males and 5 of 10 females in the 128 ppm group and 2 of 10 females in the 64 ppm group. There were no exposure-related reproductive effects noted. The authors concluded that under the conditions of the study formic acid inhalation resulted in "no significant evidence of systemic toxicity", and that respiratory tract alterations were consistent with effects produced by irritant chemicals administered by inhalation. The no observed adverse effects level (NOAEL) was determined to be 32 ppm, and this level stood as valid following peer review by the NTP Technical Reports Review Subcommittee. At thirteen weeks, this study meets the minimum duration necessary to derive an RfC-based ITSL.

In the study discussion, the principal investigator pointed out that differences exist in the susceptibility of rodents and humans to methanol toxicity; this is largely due to the fact that humans metabolize formate less readily than do rodents. Since methanol exerts its toxic effect via conversion to formate, rodents would be expected to be less susceptible to the systemic toxic effects of formic acid than humans, as they can metabolize it more rapidly. This led the principal investigator to urge caution in extrapolating the results of this study to predict the risk of systemic toxicity in humans due to formic acid exposure. However, it is important to note that during the peer-review process at NTP, one of the principal reviewers expressed concern that "the report may over-emphasize that rodent data on formic acid exposure may not be applicable to humans". The reviewer stated that the localized toxic effects observed might be very relevant for humans. Conversations with EPA (Guth, 1995) were initiated to clarify the appropriateness of cross-species extrapolation. While the potentially greater sensitivity of humans was noted by EPA as a point of uncertainty in the risk assessment, Dr. Guth indicated support for the use of the NTP bioassay as the key study, and of nasal irritation as the critical health effect. Notably, a standard ten-fold uncertainty factor is included in this RfC/ITSL derivation to account for uncertainties inherent in interspecies extrapolation.

Per section 4.1.1 (p. 4-8) of the EPA Interim Methods for Development of Inhalation Reference Concentrations (EPA, 1990), since this study recorded NOAELs

at multiple dose response levels in the absence of additional inhalation data, the highest NOAEL, *i.e.*, 32 ppm is used to drive the RfC.

Human Equivalent Concentration (HEC) Calculation:

a) The key study NOAEL of 32 ppm is converted to mg/m^3, using the chemical-specific conversion factor (1 ppm = 1.91 mg/m^3) of Verschueren (1983). Thus, the NOAEL = 61.12 mg/m^3.

b) Dose adjustment is necessary to account for discontinuous exposure regimens used in the key study. Per EPA (1990), section 4.1.1.2, p. 4-13:

$$NOAEL_{(ADJ)}\,(mg/m^3) = 61.12\ mg/m^3 \times \frac{6.5\ hrs/day}{24\ hrs/day} \times \frac{5\ days/week}{7\ days/week}$$

$$= 61.12\ mg/m^3 \times 0.27 \times 0.71 = 11.72\ mg/m^3$$

c) Since the critical toxic action of formic acid vapor is irritation, the HEC is determined assuming respiratory tract effects. Under the conditions of the NTP study, exposure related histopathological lesions were limited to the nose. Given the fact that formic acid is reactive (rather than soluble) at the site of action, Regional Gas Doses (RGDs) need to be calculated per page 4-24 of the EPA guidelines (1990). Consequently,

$$NOEL_{(HEC)}\,(mg/m^3) = NOEL_{(ADJ)}\,(mg/m^3) \times \frac{RGD_{animal}}{RGD_{human}}$$

where RGD_{animal}/RGD_{human} is the ratio of regional gas doses (RGDR) in the test animal species to that in humans for the region of interest for the toxic effect. Per EPA (Guth, 1995; IRIS, 1991,1993), the RGD for each species is determined:

$$RGD = \frac{M_V}{S}$$

where M_V is the ventilation rate (m^3/day) and S = regional surface area (cm^2) of toxic effect observed. The values of M_V are specific to sex, species, strain and duration of the experiment. In this case, since the toxic effects observed in the NTP study were all in the nose, the value used for S reflects the surface area of the extrathoracic (ET) airways (which includes the nasopharyngeal, laryngeal and gastrointestinal fractions). Since both the male rats and the female mice in the NTP study recorded the same NOAEL for the same histologic lesion (minimal olfactory epithelial degeneration), the two species are assumed in this case to be equally sensitive to the irritating effects of formic acid. The RGD_{animal} used here is the mean value of the RGDs calculated by EPA for male F344 rats and female $B6C3F_1$ mice exposed subchronically to a gas with its toxic effects in the extrathoracic respiratory tract. These RGD values were obtained from conversations with Dr. Dan Guth (Guth, 1995), of the EPA Offices of Research and Development and Health Risk Assessment; the RGD for humans was obtained from RGDR calculations listed for other chemicals on the IRIS database [see the RfC documentations for acrolein (107-02-8) and 1,3-dichloropropene (542-75-6) (IRIS 1991,1993) for examples].. So,

$$RGD_{rat} = \frac{0.19\ m^3/day}{11.6\ cm^2} = 0.016$$

$$RGD_{mouse} = \frac{0.04\ m^3/day}{2.9\ cm^2} = 0.014$$

$$RGD_{human} = \frac{20\ m^3/day}{177\ cm^2} = 0.113$$

The RGD_{animal} and RGDR are thus determined

$$RGD_{animal} = \frac{(RGD_{rat} + RGD_{mouse})}{2} = \frac{(0.016 + 0.014)}{2} = 0.015$$

and

$$RGDR = \frac{RGD_{animal}}{RGD_{human}} = \frac{0.015}{0.113} = 0.133$$

Consequently,

$$NOEL_{[HEC]}\ (mg/m^3) = NOEL_{[ADJ]}\ (mg/m^3) \times \frac{RGD_{animal}}{RGD_{human}}$$

$$= 11.72\ mg/m^3 \times 0.133$$

$$= 1.56\ mg/m^3$$

Inhalation Reference Concentration (RfC) calculation:

Per EPA (1990), section 4.1.1, pp. 4-4 to 4-5:

$$RfC = NOAEL_{[HEC]} / (UF \times MF)$$

$$= \frac{1.56\ mg/m^3}{([10 \times 10 \times 10] \times 1)} = 0.002\ mg/m^3$$

where the total UF of 1000 is composed of 3 10-fold uncertainty factors to account for extrapolation from average healthy humans to sensitive humans, for interspecies extrapolation from rats and mice to humans, and extrapolation from the subchronic NOAEL of the NTP study to a chronic NOAEL (since no longer term studies were available). The MF assumes the default value of 1.

Derivation of the ITSL:

Per section R 336.1232, rule 232, subrule (1)(a) of Act 348, the ITSL for formic acid equals the inhalation RfC. Therefore:

$$ITSL = RfC = 0.002\ mg/m^3 \times \frac{1000\ \mu g}{1\ mg} = 2\ \mu g/m^3$$

and per rule 232(2)(b), a **24 hour averaging time** applies.

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