MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

February 28, 2005

TO: File for methyl formate (CAS #107-31-3)

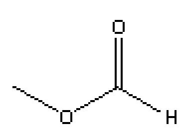
FROM: Anne Kim, Air Quality Division, Toxics Unit

SUBJECT: Screening Level Derivation

The initial threshold screening level (ITSL) for methyl formate is 1250 µg/m³ based on an 8-hour averaging time.

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, Registry for Toxic Effects of Chemical Substances, American Conference of Governmental and Industrial Hygienists Threshold Limit Values, National Institute for Occupational Safety and Health Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, Chemical Abstract Service (CAS) - Online (1967 – 2004), National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. The EPA has not established a reference concentration or reference dose for methyl formate. The molecular weight of methyl formate is 60.05 g. The molecular structure of methyl formate is shown in Figure 1.

Figure 1

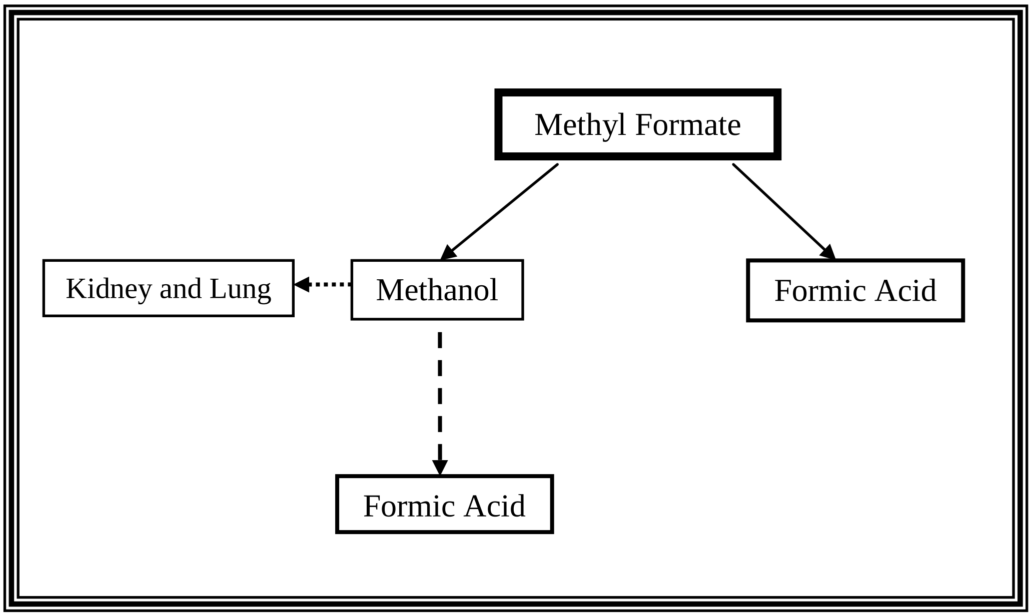


Background

An interim initial threshold screening level (ITSL) of 2.5 mg/m^3 was established September 22, 1993 (Bush, 1993). The interim ITSL was derived using the then available TLV-TWA occupational exposure limit (OEL) of 100 ppm (250 mg/m^3). This OEL was derived using toxicity information from a less irritating compound, methyl acetate; establishing a lower OEL than that of methyl acetate.

Methyl formate is a simple aliphatic acid ester. One of its industrial uses is acting “as a binding agent for core sand in iron foundries” (Berode et al., 2000). The metabolism of methyl formate in the body is shown in the figure below (Figure 2). It is rapidly metabolized into methanol and formic acid. The lungs and kidneys eliminate most of the methanol within a few hours, while the remaining methanol is further metabolized to additional formic acid (Sethre et al., 2000).

Figure 2. Metabolism of Methyl Formate



The NIOSH Pocket Guide to Chemical Hazards (2004) lists the current exposure limits from NIOSH and OSHA. NIOSH's recommended exposure limits (REL) are 100 ppm for the time-weighted average (TWA) and 150 ppm for the short-term exposure limit (STEL). OSHA's permissible exposure limits (PEL) are the same; 100 ppm for time-weighted average (TWA) and 150 ppm for short-term exposure limit (STEL). The immediately dangerous to life and health (IDLH) concentration given is 4500 ppm.

Human Toxicity

A few studies in humans were conducted in Switzerland. In all experiments, participants were exposed to the Swiss maximum allowable concentration (MAC) of 100 ppm. A later study used the exposure level of 100 ppm even though it was noted that the Swiss occupational exposure limit (OEL) had recently dropped to 50 ppm.

Sethre and colleagues (2000a) conducted a study exposing human subjects to the Swiss maximum allowable concentration (MAC) of methyl formate, 100 ppm, for 8 hours. There were a total of 40 participants; 20 in the exposure group and 20 in the control group. Because the odor threshold is at 2000 ppm and the exposure concentration was at only 100 ppm, the subjects did not known in to which group they were assigned. A number of endpoints were measured: mood, neurobehavioral performance, vision, postural sway, electromyography (EMG) of the forehead and of the neck during undemanding and demanding performance tasks, spirometry, and odor perception threshold. Only two parameters resulted in significant changes compared to control. Out of the 10 mood factors measured by the Profile of Mood States (POMS), fatigue was significantly increased in the exposed group in the evening. Control subjects also showed increased fatigue in the evenings, however, this "normal" increase in fatigue was amplified by a factor of 3 in the exposed group ($P<0.05$). The other parameter showing a significant exposure-related effect was electromyography measurements of the forehead during a demanding task. Electromyography measurements of the forehead in the control group showed an opposite pattern/trend of results compared to the exposed group. Compared to the exposed group, the control group's electromyography measurements started out lower in the morning, increased to be higher at noon, and decreased to be lower again in the evening. The study authors briefly mentioned that the electromyography measurement differences may be associated with the subjective feeling of fatigue.

One study focused on the urinary metabolites of methyl formate, methanol and formic acid, after either industry workers or participants were exposed to methyl formate (Berode et al., 2000). Another study measured urinary levels of methanol and formic acid as well as performing neurobehavioral tests on foundry workers (Sethre et al., 2000). The workers were, however, co-exposed to isopropanol in addition to methyl formate.

A toxicokinetic modeling study used the Berode et al. (2000) and Sethre et al. (2000b) occupational and controlled exposure study results to support the model developed to describe the metabolism of methyl formate and excretion of methanol and formic acid after methyl formate exposure (Nihlen et al., 2000). Conclusions based on the toxicokinetic modeling results recommended that the OEL of 100 ppm be reduced to 50 ppm to protect the public from the health effects associated with the metabolites of methyl formate, methanol and formic acid. Methanol has an OEL value of 200 ppm, and the toxicokinetic model predicted urinary excretions of 0.74 mM methanol and 0.92 mmol/g creatinine formic acid from methanol exposure. At the OEL value of 100 ppm for methyl formate, the toxicokinetic model predicted urinary excretions of 0.22 mM methanol and 2.3 mmol/g creatinine formic acid, while at a level of 50 ppm of methyl formate, the model predicted 0.14 mM methanol and 1.0 mmol/g creatinine formic acid (Table 1).

Table 1. Toxicokinetic model predictions of methanol and formic acid concentrations after methyl formate exposure

	100 ppm Methyl Formate (OEL)	50 ppm Methyl Formate (OEL ÷ 2)	200 ppm Methanol (OEL)
mM methanol	0.22	0.14	0.74
mmol/g creatinine formic acid	2.3	1.0	0.92

Formic acid concentrations were used as the critical end point because of its association with methanol toxicity as well as its association to methyl formate exposure. The concentrations of formic acid resulting from exposure to 50 ppm methyl formate and 200 ppm methanol are very similar. Thus, the study authors recommended a lower OEL of 50 ppm for methyl formate.

Discussion

The current OEL for methyl formate is 100 ppm in the United States. Under the provision of Rule 232(1)(c), an initial threshold screening level (ITSL) can be derived using this OEL. In a study conducted by Sethre et al. (2000a), however, exposure to 100 ppm of methyl formate was shown to result in changes in perception of fatigue significantly different from that of control. Thus an uncertainty factor will be added to the calculation of the ITSL. As for the numerical value of the uncertainty factor, the results from the toxicokinetic modeling study were analyzed. The model's predictions of methanol and formic acid concentrations in urine after methyl formate exposure correlated in agreement with actual measured urinary concentrations from occupational and controlled exposure studies (Nihlen et al., 2000). Modeling results supported that the OEL for methyl formate be decreased, recommending the OEL be set at 50 ppm or less. This two-fold decrease was based on the known toxic effects associated with the metabolites, methanol and formic acid. Thus, the uncertainty factor to account for the effect of increased fatigue observed in the Sethre et al. (2000a) study will be set at a value of 2.

Derivations of Screening Level

The occupational exposure level value of 100 ppm (250 mg/m^3) will be used to calculate the ITSL as promulgated in Rule 232(1)(c), however, due to the significant results from the study discussed above, an additional uncertainty factor of 2 will be used in the calculation.

$$ITSL = \frac{OEL}{UF}$$

>where OEL = occupational exposure limit

UF = uncertainty factor

UFs that apply: 1) mandated uncertainty factor specified in Rule 232(1)(c) = 100

2) significant effect in humans observed at the current occupational exposure limit = 2

$$ITSL = \frac{250\ mg/m^3}{100 \times 2}$$

ITSL = 1.25 mg/m^3 = 1250 ug/m^3

Therefore, the ITSL for methyl formate is 1250 ug/m^3 based on an 8-hour averaging time.

References

American Council of Governmental Industrial Hygienists (ACGIH). 1991. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th Ed. 2p.

Berode, M., Sethre, T., Laubli, T., Savolainen, H. Urinary Methanol and Formic Acid as Indicators of Occupational Exposure to Methyl Formate. *Int Arch Occup Environ Health*. 73: 410-414.

Bush, Dennis. 1993. Interoffice Communication: File for Methyl Formate (CAS No. 107-31-3). Michigan Department of Environmental Quality.

Nihlen, A. & Droz, P.O. 2000. Toxicokinetic Modeling of Methyl Formate Exposure and Implications for Biological Monitoring. *Int Arch Occup Environ Health*. 73: 479-487.

NIOSH. 1997. Pocket guide to chemical hazard. US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. NIOSH publication number 97-140.

Sethre, T., Laubli, T., Berode, M., Hangartner, M., Krueger, H. 2000a. Experimental Exposure to Methyl Formate and Its Neurobehavioral Effects. *Int Arch Occup Environ Health*. 73: 401-409.

Sethre, T., Laubli, T., Hangartner, M., Berode, M., Krueger H. 2000b. Isopropanol and Methyl Formate Exposure in a Foundry: Exposure Data and Neurobehavioral Measurements. *Int Arch Occup Environ Health*. 73: 528-536.