MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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July 19, 2018

To: File for Pivaloyl Chloride (CAS No. 3282-30-2)

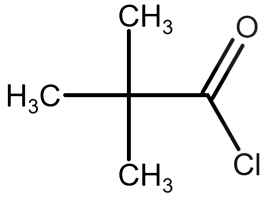
From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Screening Level Derivation

The initial threshold screening level (ITSL) for pivaloyl chloride (also known as trimethyl-acetyl chloride) is 8 µg/m³ with annual 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 (IRIS), ECHA (European Chemical Agency) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), EPA Acute Exposure Guideline Levels (AEGLs), National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels (MRLs), U.S. EPA Provisional Peer Reviewed Toxicity Values (PPRTVs) for Superfund, International Agency for Research on Cancer (IARC) Monographs, California Office of Environmental Health Hazard Assessment (OEHHA), Chemical Abstract Service (CAS) - SciFinder (1967 – May, 2018), National Library of Medicine (NLM) Toxline, and National Toxicology Program (NTP) Status Report. The EPA has not established a reference concentration for pivaloyl chloride. The ACGIH has not derived a TLV.

Figure 1. Molecular Structure of Pivaloyl Chloride



Molecular Formula: C5H9ClO
Molecular Weight: 120.58
Vapor Pressure: 27 mm Hg at 20°C

Description: Trimethylacetyl chloride is a colorless fuming liquid with a pungent odor. Very toxic by inhalation, ingestion or skin absorption. Fumes irritate the eyes and mucous membranes. Corrosive to most metals and tissue. (CAMEO, 2018)

Acute Toxicity

Groups of five male and five female Sprague-Dawley rats were exposed for one hour to 1.14, 1.47, 2.28, 2.57, 2.75 and 5.15 mg/l (1140, 1470, 2280, 2570, 2750, and 5150 mg/m³, respectively)(ECHA, 2018). Animals were kept for observation for fourteen days. Four animals (3 males, 1 female) exposed to 1.47 mg/l had pale and edematous lungs, and 2 survivors of exposure to 2.75 mg/l had mottled, red lungs. Gross necropsy findings in animals that died before study termination included signs of lacrimation, nasal discharge, polyuria, salivation, discoloration of lungs and small intestine, serosal blood vessels pronounced in small intestine and testes drawn into the abdominal cavity. There were no unusual findings at necropsy in animals exposed to 1.14 or 2.28 mg/l or survivors exposed to 2.57 mg/l. The 50 percent lethal concentration (LC50) for one hour (1-hr) was reported as 2.69 mg/l (1320 mg/m³) (95% CL: 2.57 - 2.82 mg/l).

Groups of five male and five female Sprague-Dawley rats were exposed for four hours to 1430 and 1640 mg/m³ (ECHA, 2018). Animals were observed for fourteen days. All animals exposed to 1640 mg/m³ (334 ppm) died by day 3. There were no deaths at the lower concentration 1430 mg/m³ (232 ppm). Clinical signs thought to be attributable to treatment were lacrimation, salivation, hunched posture, lethargy and respiratory distress. The signs regressed in survivors by Day 3. A small depression in weight gain during the 2 week observation period was noted in animals exposed to 1430 mg/m³ (232 ppm). All animals that died at 1640 mg/m³ (334 ppm) had increased lung weights. Gross findings at necropsy for this group included lungs that tended to remain inflated and were red or dark with white frothy fluid in the trachea. At termination, animals exposed to 1430 mg/m³ (232 ppm) had similar lung weights as controls. Necropsies of these animals were unremarkable. The four hour LC50 value was reported as between the two concentrations of 1430 and 1640 mg/m³. (ECHA. 2018)

Excerpts from NRC, 2014

> Groups of three rats were exposed to trimethyl acetyl chloride at 78 ppm (382 mg/m³) for 6 hours or at 249 ppm (1222 mg/m³) for 3.5 hours, followed by a 14-day observation period (Eastman Kodak 1992). No further experimental details were provided. Rats in the 249 ppm group exhibited dark eyes, labored breathing, loss of coordination, gasping, and jumping during exposure. All three rats exposed to 249 ppm (1222 mg/m³) were prostrate 3 hours into exposure and dead at the end of the 3.5 hours of exposure. Corneal opacity was found at death. No mortality was observed at 78 ppm (382 mg/m³). However, clinical signs including rough coat and labored breathing, and an average weight loss of 8 g in the 14-day follow-up period were observed.
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> In an RD50 irritancy test, groups of four male albino mice were exposed to trimethyl acetyl chloride at 0, 115, 180, or 634 ppm (analytic concentrations; 0, 564, 883, 3110 mg/m³) for 30 min, followed by a 24-h observation period (Hardy and Kieran 1992). Flow rate was 13 L/min, and the test atmosphere was analyzed by gas chromatography. The study followed GLP guidelines. An RD50 of 290 ppm was calculated. Mortality occurred at all test concentrations; one of four rats died at 115 ppm, three of four at 180 ppm, and three of four at 634 ppm. Absolute lung weight and relative lung-to-body-weight ratios were increased in a concentration dependent manner in animals surviving 24 h. Microscopic lung pathology in animals surviving 24

h included vascular congestion, alveolar edema, single cell necrosis of bronchiolar epithelium, alveolar duct necrosis, debris in the alveolar ducts, and generalized necrosis of bronchiolar epithelium. Because the RD50 was also associated with lethality in the test population, it was not used for the development of AEGL values. An LC50 value of 101-182 ppm (496-893 mg/m³, respectively) for 30 min was estimated by the study authors. (NRC, 2014)

Genotoxicity 1 (ECHA, 2018)
Genotoxicity: positive
Species / strain: S. typhimurium TA 1535, TA 1537, TA 98 and TA 100
Metabolic activation: with and without
Remarks: borderline result: weakly positive, result does not fit to other acid chlorides
Cytotoxicity: yes
Remarks: 500-1000 µg/plate (standard plate); 250 µg/plate (preincubation)
Vehicle controls valid: yes
Positive controls valid: yes
Other remarks on result strain/cell type: Preincubation test: S. typhimurium TA 100 without metabolic activation
Remarks: Migrated from field 'Test system'. (ECHA. 2018)

Genotoxicity 2 (ECHA, 2018)
Genotoxicity: negative
Species / strain: E. coli WP2 uvr A
Metabolic activation: with and without
Cytotoxicity: yes
Remarks: 500-1000 µg/plate (standard plate); 250 µg/plate (preincubation)
Standard plate test: there was no mutagenic effect of the test material in any of the S. typhimurium or E. coli test strains, neither in the presence nor in the absence of metabolic activation. Preincubation test: except S. typhimurium TA100, there was no mutagenic effect of test material in any of the S. typhimurium or E. coli test strains, neither in the presence nor in the absence of metabolic activation. (ECHA. 2018)

Summary of Lethal Concentration Data
See the table below for information about deaths from exposure to trimethyl acetyl chloride.

Table 1. Summary of the Lethal Concentration Data

	Study 1	Study 2	
	4-hr	3.5-hr	6-hr
100% Mortality	1640	1222	
0% Mortality	1430		382

Study 1: ECHA, 2018
Study 2: Eastman Kodak, 1992; Hardy and Kieran, 1992

Derivation of ITSL
As shown in Table 1 (above), Study 2 (Eastman Kodak, 1992) showed that all rats died after 3.5 hours of exposure to trimethyl acetyl chloride at 1222 mg/m³, but no rats died after 6

hours of exposure to 382 mg/m³. Study 1's no-effect-level of 1430 mg/m³ would not be protective of mortality effects since the lower concentration of 1222 mg/m³ from Study 2 shows 100% mortality; therefore, Study 2 was chosen as an appropriate point of departure for calculating a health protective screening level for trimethyl acetyl chloride.

Typically, a screening level would be derived from a 4-hr LC50 as prescribed in Rule 232(1)(f). However, Study 2 only used two dose groups that showed either 100% (LC100 at 1222 mg/m³) or no mortality, with a lethal concentration zero percent (or LC0) at 382 mg/m³. Using a lethal concentration study where no mortality was observed for ITSL derivation has been deemed as appropriate in certain cases. The LC0 would be used as a surrogate LD50. Use of this value is expected to provide a conservative estimate of the ITSL. However, since the resulting ITSL based on the surrogate LC50 would be higher than the default ITSL of 0.1 µg/m³ the ITSL based on a surrogate LC50 provides a more reasonable estimate of toxicity than the default.

In lieu of an LC50, as required in Rule 232(1)(h), using an LD0 instead of an LC50 results in a lower ITSL since the LC50 would likely be higher if it was available. Pursuant to Rule 232(1)(f), the ITSL was calculated from the LC0 of 382 mg/m³ as a surrogate LD50 as follows:

ITSL = LC50/(500 x 100) x unit conversion
ITSL = (382 mg/m³)/(500 x 100) x 1000 µg/mg
ITSL = 7.64 µg/m³ ≈ 8 µg/m³ (rounding to one significant figure)

The ITSL derived from Rule 232(1)(f) is given an annual averaging time (Rule 232(2)(c)).

References

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