MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

October 25, 2000

TO: Files for Copper Sulfate, pentahydrate (CAS#7758-99-8)
Copper Sulfate, anhydrous (CAS#7758-98-7)

FROM: Mary Lee Hultin, Toxics Unit, Air Quality Division

SUBJECT: Screening Level(s) for Copper Sulfate, pentahydrate (CAS#7758-99-8) and Copper Sulfate, anhydrous (CAS#7758-98-7)

The screening levels for both of the above-mentioned copper compounds are 10 $\mu g/m^3$ based on 8 hour averaging.

In 1994, the Air Quality Division (AQD) established an interim screening level for Copper Sulfate. In an effort to finalize the screening level, an updated search of the literature was performed. During the updated search, it became apparent that studies on Copper Sulfate some times covered both anhydrous and pentavalent forms. The following references or databases were searched to identify data to determine the screening level: IRIS, HEAST, NTP Management Status Report, RTECS, EPB-CCD, EPB library, CAS-online, NLM-online, IARC, NIOSH Pocket Guide, and ACGIH Guide. The U.S. Environmental Protection Agency (USEPA) has not developed a reference dose or reference concentration for either form of Copper Sulfate.

Copper Sulfate-anhydrous occurs as a grayish-white to greenish powder. The pentahydrate form occurs as blue/green crystals. Copper Sulfate pentahydrate is the usual commercial form (see CAS# 7758-99-8). Copper Sulfate is often found in combination with other pesticides (Bordeaux mixture is Copper Sulfate neutralized with hydrated lime) and is available as a dust, wettable powder, or liquid concentrate (EXTOXNET, 1996). It formerly was used as an emetic due to irritant qualities. Uses include: horticultural fungicide, algaecide, and herbicide. It is used to kill slugs and snails in irrigation and municipal water treatment systems, and as a food additive. Other uses include germicide, a therapeutic agent in veterinary medicine, and use in electroplating. (EXTOXNET, 1996; Hébert, 1993; NIOSH, 1982)

Oral data will not be used in the derivation of screening levels for Copper Sulfate, pentahydrate (CAS#7758-99-8) or for Copper Sulfate, anhydrous (CAS#7758-98-7). Copper is an essential dietary element for humans. Copper Sulfate is used as a nutritional supplement in animal hygiene. Patty's Industrial Hygiene and Toxicology, 4th edition notes that reported toxic effects from Copper via ingestion in humans result from suicide attempts and in individuals with impaired Copper metabolism (e.g., Wilson's disease). Therefore, although subchronic oral studies are available, they will not be used in this risk assessment.

All inhalation data found was used in the development of the Threshold Limit Value by the American Conference of Governmental Industrial Hygienists. The ACGIH TLV for Copper Sulfate (1.0 mg/m^3) is based upon that for copper dusts and mists. The NIOSH REL and the OSHA PEL are also 1.0 mg/m^3. Information described in the documentation of TLVs was taken from studies on both anhydrous and pentahydrate forms. The following studies were described in the Documentation of the TLVs for Copper fume and Copper Dusts and Mists:

> Male and female CD_1 mice (3-4 wk. old, number unknown) were exposed individually to an aerosol of Copper Sulfate, then group-housed, and various health parameters

compared to determine the most sensitive indicators of toxic effects following exposure to metallic sulfate aerosols. The low, intermediate, and high sulfate concentration means were 0.43, 0.93, and 2.53 mg/m^3, respectively. All exposure levels increased the mortality rate and decreased the mean survival time of both sexes of mice **challenged with streptococcus** aerosol following a single 3-hour sulfate exposure. No changes in mortality were observed when mice were challenged with streptococcus aerosol following 5 daily 3-hour exposures to 0.09 mg sulfate/m^3, but, following 10 daily exposures to 0.10 mg sulfate/m^3, mortality rate increased and survival time decreased significantly. Scanning electron microscopy of mice exposed to a single high dose revealed crystalline particles scattered throughout the respiratory system. Dose-related damage at the alveolar level was detected in the multiple-exposure animals. Differences in bacteria-induced mortality rate appeared to be the most sensitive and consistent indicators of toxicant damage. (Drummond *et al.*, 1986)

Human reports of granulomatous and fibrotic changes have been reported from vineyard workers exposed to the Bordeaux mixture. Bordeaux mixture, a 1.0-2.5% Copper Sulfate solution neutralized with hydrated lime, is used in the horticulture field for the prevention of mildew. It is no longer used in the U.S., but European vineyards still use it commonly. It may be sprayed up to 14 times per season (April through July). Sprayers can develop “vineyard sprayer’s lung,” a granulomatous pneumonitis. Symptoms include a progressive weakness, anorexia, weight loss, and dyspnea. Cough is a variable finding. The lungs of the patients show greenish-blue patches on the surface that may run together and involve most of the lung. Whole lobes may be involved, and in some cases irregular cavities are formed, similar to those found in coal miner’s pneumoconiosis. Some patients experience improvement while others worsen over time. (Levy, 1994; Pimentel and Marques, 1969; Villar, 1974)

Villar (1974) followed 15 patients hospitalized with differing clinical diagnoses (pigeon fancier’s lung, Hamman-Rich syndrome, tuberculosis, pulmonary granulomatosis, and vineyard sprayer’s lung) which were all ultimately classified as vineyard sprayer’s lung cases. All patients (14 men and 1 woman, ages 35 to 76 with average age at 54) had a history of exposure to inhalation of Bordeaux mixture. The woman had applied the mixture with a rush broom for 4 years, 43 years before the onset of the disease. The men had used manual pulverizers carried on their backs. Eleven of the men had sprayed vines until a year previously; the other 3 had not been exposed for 6, 10, or 20 years. Two patients had been exposed to other pulmonary irritants (wood dust, sand, and pigeon droppings), and 7 smoked. The most frequent clinical symptoms were general in which weakness, loss of appetite, and marked weight loss predominated. These were followed by progressive breathlessness, with or without cough. The most common x-ray picture revealed a diffuse, micronodular dissemination or a reticulonodular shadowing, predominantly in the lower portions of both lungs. There was a high incidence of cancer in this study group. A diagnosis of vineyard sprayer’s lung should always be confirmed histologically, with demonstration of the presence of Copper within the lesions. (Villar, 1974)

Pimentel and Menezes (1975) studied 3 male patients in their 50’s who had been exposed occupationally to Bordeaux mixture. It was noted that one patient was an alcoholic and a second was a moderate drinker. The men had been hospitalized for dyspnea, in one case, or for flu-like symptoms. X-rays showed involvement of the lungs, and autopsy/biopsy results indicated vineyard’s sprayer lung disease. Due to hepatic enlargement, liver samples were taken and examined histologically. Changes were found consisting of proliferation and diffuse swelling of Kupffer’s cells, sometimes showing a tendency to gather in clusters, and the formation of well-defined histiocytic or sarcoid-type granulomas. These lesions were always found near the portal tracts and contained Copper. Only the changes seen in the alcoholic patient were also associated with cirrhosis. (Pimentel and Menezes, 1975)

Case studies by Pimentel and Marques (1969) of 2 patients who were vineyard sprayers showed one worker with respiratory symptoms and one without, only being diagnosed after x-ray. (The second patient had not been spraying vineyards for over a year.) Both patients were initially considered tuberculous and underwent thoracotomies when they did not respond to treatment. The thoracotomies revealed intensely blue visceral pleura. The pulmonary lesions seemed to progress through 3 histological stages: intra-alveolar desquamation of macrophages, formation of predominantly histiocytic granulomas in the septa, and the healing of the lesions under the form of fibro-hyaline nodules. The lesions were experimentally reproduced in guinea pigs. (Pimentel and Marques, 1969)

As noted above, no existing USEPA Reference Concentration was found for Copper salts, nor is there sufficient data to derive an RfC. The oral data is inappropriate for screening level development. The human data regarding vineyard sprayer's lung and animal inhalation data were considered in the derivation of the TLV. Therefore, the TLV (for Copper Dusts and Mists) will be used for screening level derivation for both the anhydrous (CAS# 7758-98-7) and pentavalent (CAS# 7758-99-8) forms of Copper Sulfate.

ITSL = (TLV/100) * 1000

ITSL = (1 mg/m^3/100) * 1000

ITSL = 10 $\mu g/m^3$ based on an 8 hour averaging time

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