MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

April 17, 2003

TO: Catherine Simon, Chief, Toxics Unit, Air Quality Division

FROM: Marco Bianchi, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level of Turpentine (CAS #8006-64-2), and selected monoterpenes: α-pinene (CAS #80-56-8), β-pinene (CAS #127-91-3), Δ^3-carene (CAS #13466-78-9)

It is recommended that the Initial Threshold Screening Level (ITSL) for turpentine, along with select monoterpenes (α-pinene, β-pinene, and Δ^3-carene) be set at 1120μg/m^3 based on an 8-hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: Integrated Risk Information System online, Health Effects Assessment Summary Tables, National Toxicology Program (NTP) Management Status Report online, Registry for Toxic Effects of Chemical Substances, Environmental Protection Bureau (EPB) Chemical Criteria Database, EPB library, Chemical Abstract Service (CAS) online, National Library of Medicine online, International Agency for Research on Cancer (IARC) online, National Institute for Occupational Safety and Health Pocket Guide, and American Conference of Governmental Industrial Hygienists (ACGIH) Guide.

Turpentine is a general term for the crude oleoresin obtained from the soft wood conifers. It is a mixture of substances, mostly terpenes (58-65%), which vary in composition by the country and tree of origin. Terpenes are a ubiquitous group of over 4000 natural compounds, derived from units of isoprene (2-methyl-1,3-butadiene). Major components of turpentine are α-pinene, β-pinene, Δ^3-carene, and d-limonene, which are bicyclical monoterpenes with the empirical formula of $C_{10}H_{16}$. Older preparations tend to contain high concentrations of Δ^3-carene. In addition, sesquiterpenes such as β-phellandrene, cadinene, and longifolene can be found in turpentine although usually only in small quantities.

Turpentine is a light, volatile, essential oil obtained from resinous exudates or resinous wood associated with living or dead coniferous trees. Several types of turpentine are recognized in commercial trades (such as gum spirits of turpentine, steam-distilled wood turpentine, destructively distilled (carbonized) wood turpentine, and sulfate wood turpentine). Gum turpentine is a yellowish, opaque, sticky mass with a characteristic odor. Wood turpentine is a colorless liquid with an aromatic, unpleasant, penetrating odor reportedly having a threshold of 75 to 100 ppm; the odor becomes more pronounced with aging or exposure to air.

Pharmacokinetics/Metabolism Studies

Turpentine is absorbed following oral, dermal, and inhalation exposure. α-Pinene is readily

absorbed from skin; maximum blood concentrations are reached after only ten minutes, and blood concentrations are a direct function of the amount of skin exposed. It is eliminated unchanged in expired air and in urine, as well as a glucuronic acid conjugate in urine. Sperling[1] reported that a considerable portion of inhaled turpentine is found in various parenchymal organs and the brain. Absorbed turpentine is metabolized at least in part through oxidation by the cytochrome P-450 system.

Filipsson (1996)[1] exposed eight healthy volunteer men without occupational solvent exposure for two hours during light physical exercise (bicycle ergometer) at 449 mg/m^3 of turpentine and on different days to 10 mg/m^3 of Δ^3-carene as a positive control. Blood, expiratory air, and urine samples were collected. The mean relative uptakes of α-pinene, β-pinene, and Δ^3-carene from turpentine exposure were 62, 66, and 68% respectively. Between 2 and 5% of the net uptake was excreted unchanged in expired air at the end of the exposure. Mean blood clearances at 21 hours after exposure were 0.8, 0.5, and 0.4 liter/kg/hr respectively; the phase mean half lives were 32, 25, and 42 hours respectively. Other similar chamber studies found these compounds had a high affinity to adipose tissues because of their long half-lives.

Human Studies

Wood dusts, particularly hardwoods more than softwoods, have been associated with allergic skin and respiratory responses, impaired respiratory function, and cancer in humans (IARC 1995, NCI 1985)[1].

There are numerous case reports and a series of accidental and intentional turpentine ingestions. The mean oral lethal dose of turpentine ranges from 15 to 90 ml, a value confirmed in reports of a number of turpentine fatalities. Aspiration can lead to chemical pneumonitis (Gurwitz 1978)[1] with pathognomonic dyspnea, acute pulmonary edema, and cyanosis; death occurs from central arrest. Glucosuria, hematuria, albuminuria, and anuria have all been recorded as a consequence of acute turpentine poisoning.

Workplace Exposures

Workers are exposed to turpentine and its monoterpene components during both the production of turpentine in the wood industry, and during the derivative production. An international database of over 31,000 exposure measurements in the pulp, paper, and paper product industries has been established by the IARC as part of a multinational study on possible cancer morbidity and mortality risks in these industries. Of these measurements, only 6% were reportedly greater than the Threshold Limit Value (TLV) of 100 ppm for turpentine.

Kauppinen (1986)[1] monitored a range of compounds in 19 Finnish plywood plants from the 1960s to the 1980s. In addition to glues, wood dust, solvents, phenol, and pesticides, terpene concentrations (α-pinene, β-pinene, and Δ^3-carene) had ranges of 0.7 to 5.5 ppm. In a 1996 report, Eriksson[1] found that personal exposure to monoterpenes in saw mills and joinery shops may exceed 27 ppm. In comparison, the British Columbia Forest Industry Health Research Program (1999)[1] evaluated terpene exposures in personal and area samples in 12 British Colombia pulp mills. Of the 63 personal samples, individual and total terpene levels were generally less than 1 ppm (the highest was 2.9 ppm primarily α-pinene). Process Engineer, Steam Plant Utility Man, and Field Operator were job titles with the highest exposure levels.

Animal Studies

The ACGIH documentation listed LC_{50} values for turpentine vapor in rats of 3590 ppm for a 1-hour exposure, and 2150 ppm for a 6-hour exposure. Signs of acute turpentine intoxication included ataxia, tremor, convulsions, tachypnea, decreased tidal volume, and death due to

sudden apnea. No pulmonary lesions could be seen at necropsy. Tissue analysis found the highest concentration of turpentine components in the spleen and brain.

Savolainen and Pfaffli (1978)[1] exposed 40 male adult male Wistar rats to 300 ppm of commercial turpentine for 6 hours/day, 5 days/week, for 8 weeks with a group of negative control litter mates. No appreciable behavioral changes were observed. There was accumulation of α-pinene measured in the perinephric fat and brain.

Smyth and Smyth[1] evaluated the potential toxicity of steam-distilled turpentine vapor in guinea pigs that inhaled 715 ppm, 4 hours/day for 45 to 58 days. Neither significant hematologic changes nor any pathology attributable to turpentine exposure could be detected. No injury was found in dogs that inhaled 180 ppm, 3.5 hours/day for 8 days.

Lastbom et al., (2000)[1] used a group of 8 female Dunkin Hartley guinea pigs, sensitized by dermal exposure through an intradermal injection of Δ^3-carene to perform a modified Cumulative Contact Enhancement Test protocol with a separate control group of 8 female guinea pigs. The authors concluded that skin sensitization may increase lung reactivity to Δ^3-carene with important mediators of this effect apparently present in the blood. Hellerstrom et al., (1963), Pirila 1958, and Pirila 1969[1] showed that reaction with oxygen is necessary for turpentine to manifest its potential to cause eczema in pigs and other experimental animals. Further work identified Δ^3-carene oxidation, rather than α- and β-pinene, as the main source of the eczematous potential after oxidation of the compound in pigs and humans.

Carcinogenicity

There is very little data available on the carcinogenic potential of turpentine and its monoterpene derivatives in the literature. Turpentine reportedly enhanced the tumorigenicity of tar in skin painting studies in rabbits, but not in skin painting studies in mice for benzo[a]pyrene or 7,12-dimethylbenz[a]anthracene. Cooper (1956)[1] found that turpentine was not carcinogenic in mice. The NTP studies concluded that d-limonene is clearly carcinogenic in male rats; however, the carcinogenicity was attributable to α_2-u-globulin renal toxicity, not considered relevant to human carcinogenicity (NTP).

Reproductive/Developmental

Five female adult Sprague-Dawley rats exposed to an unreported level of "turpentine vapors" for 10 minutes twice/day in a chamber during days 17 to 21 gestation, produced 59% dead newborns compared to zero in the 3 unexposed controls, and 20% in 5 rats similarly exposed to thinner at an unknown level. Of note, incoordination, salivation, ataxia, and polypnea were noted in the adults 5 minutes after exposure, although some reportedly developed an excitatory subanaesthetic stage and immediate recovery following exposure. Growth of the fetus was delayed, but no effects on the neonate body size were reported. No histologic alterations were reportedly seen in the cerebral cortex of the newborn rats. In several reproductive studies in rabbits, rats, and mice, d-limonene did not cause fetal toxicity or developmental toxicity except at doses toxic to the pregnant animals (WEEL, 1993).[1]

Genotoxicity Studies

There are almost no data available on the genotoxicity of turpentine and the monoterpenes. NTP studies showed that d-limonene and its metabolites were not mutagenic in Ames testing using Salmonella with and without metabolic activation, nor was there evidence of genotoxicity in mouse lymphoma or Chinese Hamster Ovary assays.

Skin

As early as 1926, there have been published reports of turpentine causing occupational dermatitis. Turpentine can cause both allergic and non-allergic contact dermatitis. Turpentine is a skin irritant and skin contact may cause eczema; turpentine has traditionally been used in numerous dermatologic diagnostic patch tests. Workers in the chemical, rubber, and welding industries exposed to turpentine have developed contact dermatoses.

Hellerstrom et al., (1963)[1] studied 10 individuals with healthy skin and confirmed that oxidized Δ^3-carene is the primary cause of skin irritation with turpentine exposure. The hydroperoxide breakdown product, Δ^3-carene hydroperoxide, is thought to be the actual cause. Although Pirla et al., (1969)[1] and Lear 1996[1], have found patients who reacted to the other terpenes, it was usually at much higher levels than to the carenes. Furthermore, they reported that turpentine mixtures caused less eczema with decreasing levels of Δ^3-carene through purification.

Respiratory

Nelson[2] exposed volunteers to turpentine vapor for 3 to 5 minutes; 81 ppm caused nose and throat irritation in several subjects, and 175 ppm was intolerable for the majority of the volunteers. In this study, a majority of the subjects estimated that 100 ppm was the highest concentration which could be tolerated. In addition, Ruth (1986),[2] listed the irritating concentration of turpentine in air as 100 ppm, based on the results of controlled studies conducted by Nelson[2]. However, Kasanen et al., (1999)[1] as part of their RD_{50} mice work on turpentine and the monoterpenes, as well as human exposure studies, suggest that the irritancy threshold for α-pinene is 34 ppm and 40 ppm for Δ^3-carene.

Neurologic

There has been a large area of research, particularly in Scandinavia, looking at the neuropsychologic effects of occupational exposure to solvents. For the vast majority of these studies, turpentine has just been one of the many solvent exposures (including toluene and xylene) in these occupational groups, making it difficult to conclude anything about the particular neuropsychologic effects of turpentine.

Development of Screening Level

Prior to 2001, the TLV established by the ACGIH for turpentine was 100 ppm (556 mg/m^3), based on a study by Nelson (1943)[2]. Although this value was recommended by the ACGIH to minimize the potential for upper respiratory tract irritation for the general working population, no clear explanation was given to justify it. The TLV was not shown to be protective from all respiratory effects. Nelson found that 75 ppm of turpentine vapor caused nose and throat irritation in several subjects, and that 100 ppm was the highest concentration which could be tolerated. Due to this weak TLV justification, the Air Unit re-reviewed this compound to determine if additional information was available to provide a more scientifically justified basis for a screening level. During this review period, it was discovered that the ACGIH had placed turpentine on their list of "*Notice of Intended Changes for 2002.*" It was also discovered that they had written a draft justification document for turpentine with a newly proposed TLV of 20 ppm (112 mg/m^3).

The new draft document is *extremely comprehensive* and reviews the following topics for turpentine; chemical and physical properties, workplace exposures, animals studies (acute, subchronic, chronic, carcinogenicity, reproductive/developmental, genotoxicity studies, pharmacokinetic/metabolism studies), and human studies (case studies, neurologic, hematologic, and cancer studies). However, the draft document is labeled "do not cite"

because it is still under review by the ACGIH. The draft documentation does have a number of small grammatical errors, but the final recommendation of 20 ppm is toxicologically sound. Unlike the first justification document, the recommendation presented in the draft document is fully supported by the data. The recommendation states: *The chamber and workplace studies of turpentine and monoterpenes (with and without wood dust co-exposures) make it clear that the TLV for turpentine and its primary constituent monoterpenes must be reduced to avoid reports of acute upper respiratory tract irritation, as well as possible long term pulmonary compromise. The chamber studies show a clear effect at 80 ppm, but these were only 2-hour studies in healthy volunteers without use of the more sensitive measure of diffusing capacity. The occupational studies illustrate short and long term alveolar damage as evidenced by decreased diffusing capacity in both healthy volunteers and workers correlated with terpene concentrations above 10 ppm. However, these studies did involve additional co-exposures such as wood dust, bioactive aerosols, and other volatiles. Therefore, a TLV of 20 ppm (112 mg/m^3) for turpentine and the monoterpenes (α-pinene, β-pinene, and Δ^3-carene) is recommended to minimize the potential for upper respiratory tract irritation and long term respiratory compromise. Although skin can apparently be a significant route of absorption for turpentine, there is no evidence of end organ damage as a result of this absorption, therefore a skin designation is not recommended.* Rule 229(2)(b) states that the ITSL may be determined by any alternative methodology to assess non-carcinogenic health effects that can be demonstrated to the Department to be more appropriate, based on toxicological grounds and supported by scientific data. Considering the above information, it is recommended that the ITSL for turpentine and select monoterpenes; α-pinene, β-pinene, and Δ^3-carene be derived from the proposed TLV of 20 ppm or 112 mg/m^3. Additionally, because turpentine is comprised of one or more of a group of terpenes where the toxicity is anticipated to act via similar mechanisms, the combined ambient impact of all terpenes; α-pinene, β-pinene, and Δ^3-carene must be below this ITSL for the same air permit.

The ITSL was determined as follows:

ACGIH TLV = 112 mg/m^3

112 mg/m^3 ÷ 100 = 1.12 mg/m^3

$$1.12\ \text{mg/m}^3 \times \frac{1000\ \text{ug/m}^3}{1\ \text{mg/m}^3} = 1120\ \text{ug/m}^3$$

The ITSL for turpentine and α-pinene, β-pinene, and Δ^3-carene = 1120 ug/m^3 based on an 8-hour averaging time.

References:

1. Documentation of TLVs and Biological Exposure Indices. 2002. Draft of Turpentine and Selected Monoterpenes (α-pinene, β-pinene, and Δ^3-carene). ACGIH..

2. Documentation of TLVs and Biological Exposure Indices. 1991. Turpentine. ACGIH.