MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

September 20, 1999

TO: File for Phenyltrimethoxy Silane (PTMS) (CAS# 2996-92-1)

FROM: Dan O'Brien, Toxics Unit, Air Quality Division

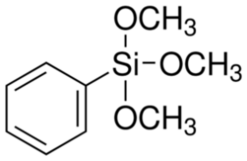
SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for phenyltrimethoxysilane is 60 µg/m^3 based on an annual averaging time.

The following references or databases were searched to identify data to determine the ITSL: AQD chemical files; EPA's Integrated Risk Information System (IRIS) and Health Effects Assessment Summary Tables (HEAST); American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) Booklet; National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Chemical Hazards and Registry of Toxic Effects of Chemical Substances (RTECS): National Toxicology Program (NTP) World Wide Website (WVVW), MDEQ Library; International Agency for Research on Cancer (IARC) WWVV; Chemical Abstract Service (CAS) On-line and National Library of Medicine (NLM) Toxline (1967—October 6, 1998), Chemical Evaluation Search And Retrieval System (CESARS), Handbook of Environmental Data on Organic Chemicals, Patty's Industrial Hygiene and Toxicology, Merck Index and the Condensed Chemical Dictionary.

Hawley (1981) describes PTMS as being a combustible liquid used in polymers to be applied to powders, glass, paper and fabrics. No other description of the compound was found in our searches. The compound's molecular structure (CambridgeSoft, 1999) is displayed in Figure 1.

Figure 1.



Searches of the toxicologic literature unearthed only one reference to the toxicity of PTMS, a citation for an acute intravenous lethal dose 50 (LD50) in mice of 180 mg/kg (RTECS, 1998). However, because the Air Toxics Rules do not provide a means for extrapolating measures of toxicity by this route of exposure to human health risks from inhalation exposures, this citation cannot be used as the basis for derivation of a screening level.

However, conversations with the Product Safety Toxicologist at Dow Corning Corporation (Hoffman, 1998) resulted in identification and acquisition of an unpublished twenty day inhalation toxicity study of PTMS in rats (Breckenridge et aI., 1980) which was of sufficient rigor for use as the basis of a screening level. In that study, groups of ten male and ten female Sprague-Dawley rats, aged 12-16 weeks and weighing 200-250 g, were randomly assigned to experimental groups which were exposed to technical grade PTMS vapor in inhalation chambers by whole body exposure at concentrations of 0 (air controls), 10, 50 or 80 ppm (0, 81, 406 and 649 mg/m³, respectively)[1], 7 hours/day, 5 days/week for four weeks. Animals were individually housed and had ad libitum access to standard commercial laboratory diet and tap water. Concentrations of PTMS in each of the four exposure chambers were calculated nominally using air flow and weight loss from the gas generators, and confirmed with hourly measurements using an infrared gas analyzer. Physiological parameters monitored included clinical observations, body weights (measured twice weekly), absolute (g/rat-day) and relative (g/kg body weight-day) food consumption, hematology[2], urinalysis[3] and serum biochemistry[4] (on samples collected immediately prior to sacrifice), gross and histopathology[5], organ weights[6] and bone marrow cytology/histopathology. Statistical comparisons of continuous data between groups employed Dunnett's test, with a 5% level chosen as indicative of a significant difference.

Average actual chamber exposure concentrations were 2.0, 11.5, 54.6 and 78.6 ppm (16.2, 93.3, 442.9 and 637.5 mg/m³) in the control, low, mid and high dose groups, respectively. Noting that the infrared analyzer recorded detectable concentrations of test article in the control chamber even though no agent was introduced into it, the authors concluded that vapors from rat urine and feces were causing infrared absorbance at the analytical wavelength. Thus, they suggested that actual chamber PTMS concentrations should be considered 2 ppm (16.2 mg/m³) lower than those recorded. This adjustment would make the effective average chamber concentrations 0, 77.1, 426.7 and 621.3 mg/m³ in the control, low, mid and high dose groups, respectively, over the course of the study. During the second week of exposure, half of the animals in the mid dose group were sprayed with PTMS because of an improperly connected compressed air hose. Four animals were saturated, became ataxic and semi-conscious within 45 minutes. One female died within eight hours, and the remaining three rats were all dead

[1] Exposure concentrations are converted from parts per million (ppm) to mg/m³ using the equation: Exposure concentration (mg/m³) = [Exposure concentration (ppm) x Molecular weight]/24.45. Thus, e.g., the target concentration in the high dose group would be [80 x 198.32] ÷ 24.45 = 649 mg/m³.
[2] Erythrocyte count, hemoglobin concentration, hematocrit, total and differential leucocyte counts. Animals were unanesthetized and fasted overnight at the time of sampling.
[3] Assessed for color, volume, odor, transparency, specific gravity, occult blood, ketones, glucose, protein, pH, bilirubin, and microscopic examination of sediment following centrifugation. Urine was collected overnight, on ice.
[4] Glucose, blood urea nitrogen, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. Animals were anaesthetized and fasted overnight at the time of sampling.
[5] Brain (cerebrum, cerebellum, medulla and pons), spinal cord, olfactory bulb/nerves, eyes/optic nerves, pituitary, thyroid, thymus, adrenals, heart, spleen, aorta, esophagus, salivary gland, stomach, duodenum, jejunurn, ileum, cecum, colon, rectum, liver, pancreas, gonads, lymph nodes (mesenteric and mediastinal), uterus, prostate, kidneys, urinary bladder, scialic nerve, skeletal muscle, skin, tongue and buccal mucosa, nasal and paranasal sinuses, nasal septum. larynx, trachea and major bronchi.
[6] Adrenal glands, brain, gonads, heart, kidneys, liver, pituitary, spleen, lungs and thyroid.

by the next morning. The six rats that were sprayed but not saturated experienced decreased food consumption with consequent weight loss, from which they eventually recovered. The circumstances surrounding the deaths of the four saturated animals led the authors to attribute the clinical signs and fatalities to the acute dermal toxicity of PTMS.

With respect to clinical observations, a low percentage of rats (3, 3 and 5 of 20 in the low, mid and high dose groups, respectively) in all of the exposed groups exhibited reddish brown perinasal/periorbital fur staining: this observation was also recorded in 3 of 20 control rats during the two week pre-exposure acclimation period, but not during exposure. In general, rats in all groups experienced weight gains over the period of the study, and no statistically significant differences were noted that were attributable to exposure. No significant differences in absolute food consumption were noted between the control and exposed groups, but relative food consumption was significantly increased during the final week of exposure in the mid dose females, and during the third week of exposure in the high dose females. In both cases, these increases followed periods of decreasing body weight, and were likely compensatory in nature. There were no statistically significant differences between any of the exposed groups and controls for any of the measured hematological parameters, and while variation among groups was present, it was within normal historical limits for this species (Harkness and Wagner, 1989). Results of urinalyses supported similar inferences. Serological tests recorded statistically significant increases of mean blood glucose in the low dose males as compared to those in the controls, but the differences did not persist into the two higher dose groups, nor did the value fall outside normal limits for the species. Thus, it was unlikely to have been related to PTMS exposure. Blood urea nitrogen concentrations in the control, low and high dose groups of both sexes were slightly above the range of normal for rats (Harkness and Wagner, 1989). There were no significant differences from controls for any of the other measured serological parameters at any level of exposure. Bone marrow cytology and histopathology was unremarkable.

Necropsy results recorded the most common gross lesions to be pulmonary and lymph node congestion and enlargement, and periuterine/periovarian fluid retention. These lesions were equally distributed across groups (except for fluid around the ovaries, which occurred more frequently in the low and high dose groups but was unaccompanied by any histologic lesions). Focal lung congestion of variable severity was recorded with high prevalence (60-100% of females, 70-90% of males) in all groups, including controls. Among the four mid dose group rats that died following saturation with the agent, gross lesions included congested cervical lymph nodes, thymus and thyroid, perineal blood staining, hydrometra, acute pulmonary congestion and renal medullary hemorrhages. With respect to organ weights, among males, mean left (but not right) absolute and relative adrenal weights were significantly decreased in the mid dose group. Mean absolute left adrenal weights were significantly decreased in the high dose rats as well, and mean absolute and relative splenic weights were significantly decreased in the low dose group. There were no significant differences in any absolute or relative mean organ weights among the females. Because the organ weight differences recorded in the males were small, unilateral, and/or not related to dose, they were considered unlikely to be a consequence of exposure.

Histopathological lesions were limited mainly to the lungs and lower airways, where inflammatory changes which the authors judged consistent with mild to moderate mycoplasmosis were noted in all the dose groups, including controls. Other lesions were sporadic and considered attributable to intercurrent subclinical infections and/or their sequelae. In summary, under the conditions of the study, the authors concluded that "administration of phenyltrimethoxysilane by the inhalation route at a dose of 80 ppm did not produce any systemic toxicity". Though not specified by the authors, the effective mean inhalation chamber concentration maintained at the highest exposure 3level tested (621.3 mg/m^3) could reasonably be considered a No Observed Effect Level (NOEL) for this study.

Derivation of the ITSL: In the case of PTMS, selection of a key toxicological study for use in derivation of a screening level is unusually straightforward, since the only adequate inhalation data (indeed, the only adequate data, period) found were from the unpublished repeat dose study of Breckenridge et aI. (1980). It bears mention that this study is not of ideal quality, since it did not identify a threshold for the toxicity of PTMS, nor was the purity of the technical grade test agent specified,. In addition, the subclinical mycoplasmosis which apparently occurred among the experimental animals concurrent with exposure unfortunately obscured the etiology of such clinical signs as periocular staining and decreases in food consumption/body weight which could conceivably have been attributable to PTMS exposure as well as Mycoplasma. Still, on balance, the study was well conducted, completely reported and investigated more than enough endpoints to adequately assess the potential for systemic toxicity from PTMS exposure. Consequently, the Breckenridge study is used as the basis for the ITSL for PTMS. In the absence of an identified No Observed Adverse Effect Level (NOAEL), the NOEL is used as a conservative surrogate.

Applying section R 336.1232, rule 232(1)(d) of Act 451, as amended:

$$\text{ITSL} = \text{NOAEL}/(35)(100) \times (\text{hours exposed/day})/(24 \text{ hours/day})$$

The algorithm as stated in the rules is intended to apply to a study of 7 days duration, and incorporates uncertainty factors (UFs) of 35 to account for the uncertainty in using a NOAEL from a 7 day exposure period to estimate a NOAEL for a lifetime of exposure, and 100 to account for uncertainties in extrapolating from animals to humans, and to unusually sensitive individuals in the human population (MDNR, 1989). As specified by the rule, the algorithm can also be used on a case by case basis to derive ITSLs using studies of exposure durations other than 7 days. Since the Breckenridge study employed exposures of 20 days duration, the uncertainty factor for study duration is reduced here from 35 to 30.

Substituting:

$\text{ITSL} = (621.3 \text{ mg/m}^3)/(30)(100) \times (7 \text{ hours/day})/(24 \text{ hours/day})$
$\text{ITSL} = (0.207 \times 0.292) = 0.060 \text{ mg/m}^3 \times 1000 \mu\text{g/mg} = 60.44 \approx 60 \mu\text{g/m}^3$

And per rule 232(2)(c), an annual averaging time applies.

References

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