MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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February 13, 2017

TO: File for Dimethoxydimethylsilane (CAS No. 1112-39-6)

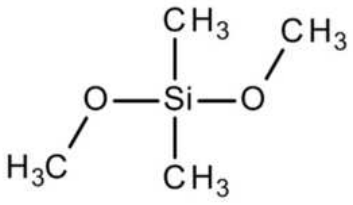
FROM: Mike Depa, Air Quality Division, Toxics Unit

SUBJECT: Derivation of Screening Level

The Initial Threshold Screening Level (ITSL) for dimethoxydimethylsilane is 90 µg/m^3 with annual averaging time.

The following references and/or databases were searched in order to find data to derive a screening level: Toxic Substance Control Act Test Submissions Simple Query for TSCATS 2.0, U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), the National Institute of Occupational Safety and Health (NIOSH), the Agency for Toxic Substances and Disease Registry (ATSDR), the Registry of Toxic Effects of Chemical Substances (RTECS), the California Office of Environmental Health Hazard Assessment (Cal OEHHA), National Library of Medicine's TOXNET and TOXLINE, Toxic Substance Control Act (TSCA) Test Submissions (TSCATS), EPA's Provisional Peer Reviewed Toxicity Values for Superfund (PPRTV), European Chemicals Agency (ECHA) Risk Assessment (REACH) database, Chemical Abstract Service (CAS) SciFinder database and US EPA (epa.gov). The molecular weight of dimethoxydimethylsilane is 120.25g. The molecular structure is shown in Figure 1.

Figure 1. Molecular Struction of Dimethoxydimethylsilane



In an acute inhalation study, 5 male and 5 female Sprague-Dawley rats were exposed to via whole-body inhalation to actual chamber concentration of 0 (zero) or 4.7 mg/l dimethoxydimethylsilane for 4 hours (REACH, 2013). Duration of observation period following administration: 14 days - Frequency of observations and weighing: Gauge readings were recorded hourly during the chamber period. Animals were observed once a day during weekdays. Individual animal body weights were taken prior to exposure and on days 7 and 14 after exposure. - Necropsy of survivors performed: Not reported -

Other examinations performed: body weight. No mortalities were observed in either groups during the exposure or post-exposure periods. Clinical signs were not reported. No apparent test material related effect on body weights (see Table 1).

Table 1. Mean Body Weight Data (grams).

Days After Exposure	Group I, Control		Test Group II	
	Males	Females	Males	Females
0	189 ± 5	183 ± 10	188 ± 5	183 ± 12
7	242 ± 8	214 ± 15	248 ± 9	205 ± 15
14	295 ± 13	233 ± 21	305 ± 15	230 ± 20

In an oral toxicity study, male and female Sprague-Dawley rats were administered by oral gavage doses of 0, 50, 250 or 1000 mg/kgBW/day for 28 to 51 consecutive days (Dow. 2010). The study animals were divided into three groups. There were 10 male rats per exposure concentration in Group 1 (male group). Rats in this group, used both to assess toxicity of the test material and for mating, were administered the test article for 29 consecutive days and then euthanized the next days There were 10 female rats per dose group in Group 2 (toxicity group females). Rats in this group were administered the test article for 28 consecutive days and then euthanized the next day for assessment of toxicity. Group 3 (reproductive group females) was comprised of 10 female rats per dose group. Rats in this group were exposed for a two week premating phase, a 14-day mating phase, and through day 3 post-partum, up to 51 days in total. Animals were observed twice daily on weekdays and once daily on weekends and holidays for mortality or morbidity. Clinical observations were performed daily immediately following exposure. Body weight measurements were performed weekly. All animals received a detailed physical examination once before the first dose (to allow for within a subject comparisons), and weekly thereafter. Additional body weights on reproductive group females were obtained on gestational days (GD) 0, 14, and 20, within 24 hours of parturition, and on post-partum day four. Individual food consumption was recorded at Least weekly, except during the cohabitation period. Functional observational battery (FOB) and motor activity evaluations were performed on males and toxicity group females once prior to initiation of exposures and during the 4th week of exposure. Blood samples for hematology and serum chemistry evaluations were collected at the scheduled necropsy from males and toxicity group females. Complete necropsies were performed on the males and the toxicity group females and selected organs were weighed. Microscopic examination was performed on protocol-specified tissues on all males and toxicity group females from the control and 1000 mg/kgBW/day dose groups. Target tissues were examined from the 50 and 250 mg/kgBW/day groups. Mating was initiated after the first two weeks of exposure by pairing reproductive group females with males of the same treatment group until positive evidence of mating was obtained. Reproductive and developmental parameters evaluated included evidence of mating, pregnancy, duration of gestation, mean lifter size, mean live litter size, mean Litter weight, and mean ratio of live births/litter size. Dams and pups were euthanized on post-partum day 4 and examined for external gross lesions. The number of corpora lutea, and the number of uterine implantation sites were determined for all reproductive group females. Oral gavage administration of dimethyldimethoxysilane in a corn oil

vehicle to male and female Sprague-Dawley rats at concentrations of up to 1000 mg/kgBW/day was generally well tolerated. For the males at 1000 mg/kgBW/day, significant abnormal observations were noted and included soiling of the chin and urogenital area. Soiling of the chin, muzzle and urogenital areas were significant abnormal observations in the toxicity group females at 1000 mg/kgBW/day. Abdominal, chin, muzzle and urogenital soiling were significant abnormal observations in the reproductive group females at 1000 mg/kgBW/day.

There were no statistically significant differences between controls and treatment groups in the mean body weights on any day for any of the three groups: males, toxicity group females, and reproductive group females. There were no statistically significant differences between controls and treatment groups in mean body weight gains for any interval for males and toxicity group females. There was a statistically significant decrease in body weight gain compared to control values for the reproductive group females during gestational week 3 and for the interval from day 1 of study to post-partum day 4 in the 1000 mg/kgBW/day group. There were no differences in the average daily food consumption between controls and treatment groups for the male and toxicity group females for any of the measured time periods. In the 1000 mg/kgBW/day reproductive group females, there was a significant decrease (35%) in food consumption during the interval post-parturn days 0-4.

No statistically significant differences were found between the control and treatment groups in either sex for all the Functional Observational Battery (FOB) ranked tests. There were no statistically significant differences between either males or toxicity group females and their respective controls for the FOB continuous test and motor activity. There were no treatment-related changes associated with dimethyldimethoxysilane administration on rat neurobiological junction as evaluated with FOB and motor activity parameters. Statistically significant changes noted in hematological parameters and prothrombin times and clinical chemistry parameters for males and toxicity group females were within or slightly above/below historical control values and these findings did not correlate with a pathological outcome, therefore, no toxicological significance is given to any of these statistically identified differences. There were statistically significant differences compared to controls noted for the following organ weights in males: adrenal glands (decrease at 1000 mg/kgBW/day), liver (increase at 250 and 1000 mg/kgBW/day), testes (decrease at 1000 mg/kgBW/day), thymus (decrease at 1000 mg/kgBW/day), epididymides (decrease at 1000 mg/kgBW/day), prostate gland (decrease at 1000 mg/kgBW/day) and seminal vesicles (decrease at 1000 mg/kgBW/day). There were statistically significant differences for the mean percentage of organ weights relative to body weights for adrenal glands (decrease at 1000 mg/kgBW/day), liver (increase at 250 and 1000 mg/kgBW/day), thymus (decrease at 1000 mg/kgBW/day) and testes (decrease at 1000 mg/kgBW/day) for the males. There were statistically significant differences noted for organ weights in toxicity group females compared to controls; liver (increase at 250 and 1000 mg/kgBW/day) and spleen (decrease at 1000 mg/kgBW/day). There were statistically significant differences for the mean percentage of organ weights relative to body weights for liver (increase at 250 and 1000 mg/kgBW/day) and spleen (decrease at 1000 mg/kgBW/day) for the toxicity group females. A standard set of protocol-defined tissues was examined for control and high-dose groups. Identified target tissues were examined for low- and mid-dose groups. Effects attributable to test article administration in males occurred in the liver,

thyroid gland, adrenal glands, kidneys, testes, and epididymides. In females test material effects were observed in the liver and thyroid glands. There were questionable effects in the spleen of males and the lungs of, both sexes. Target tissues examined at 50 and 250 mg/kgBW/day in males were liver, lungs, thyroid glands, adrenal glands, kidneys, testes, epididymides and spleen. In females, the target tissues examined were liver, lungs and thyroid glands.

In the liver, there were three primary effects of the test article observed, including panlobular hepatocellular hypertrophy in both sexes at 1000 mg/kgBW/day and centrilobular hypertrophy in females at 250 mg/kgBW/day, increased periportal hepatocellular vacuolation (microvesicular lipidosis, females administered 1000 mg/kgBW/day), and protoporphyrin accumulation (males only). The latter was usually accompanied by chronic inflammation and bile duct hyperplasia. Hepatocellular hypertrophy (panlobular or centrilobular) is considered an adaptive change. Hepatic vacuolation, unless severe, is generally considered non-adverse, Hepatic protoporphyrin accumulation is considered an adverse effect.
Thyroid follicular cell hypertrophy was observed in the thyroid gland of high-dose rats of both sexes. This is considered an adaptive secondary effect and adverse for the rat, but the mechanism is generally not applicable to species with significant levels of thyroid binding globulin (Capen et al., 2002).
There was minimal adrenal cortical atrophy in half of the male rats dosed at 1000 mg/kgBW/day. The pathogenesis and significance of this finding is not clear. In the testes there was moderate to marked seminiferous tubule degeneration observed in all 1000 mg/kgBW/day male rats that was characterized by degeneration of spermatocytes. A downstream effect was observed in the epididymides of the same rats. This is an adverse finding.
Kidney findings tabulated as protein droplet nephropathy and consistent with minimal alpha-2-µ-nephropathy (Hard et al., 1999) were observed in all male 'rats administered 1000 mg/kgBW/day. The finding was not detected in lower dose males, and, characteristically, was not observed in female rats. This is a male-rat-specific finding.

Based on initial examination of lung and spleen from control and high-dose animals, these tissues were considered possible targets; however, further examination and inclusion of animals from the mid- and low-dose groups did not support this interpretation.
The increased liver weights in males and toxicity group females at 1000 mg/kgBW/day correlated with the histopathologic finding of panlobular hypertrophy and centrilobular hypertrophy in females at 250 mg/kgBW/day. In males, adrenal cortical atrophy was accompanied by a decrease in absolute and relative adrenal weights at 1000 mg/kgBW/day, seminiferous tubule degeneration was accompanied by a decrease in absolute and relative testes weights at 1000 mg/kgBW/day, epididymal effects were accompanied by a decrease in absolute and relative decreases in epididymal weights, and kidney nephropathy findings were accompanied by an increase in relative kidney weights. In the reproductive group females, there were no statistically significant differences across treatment groups for corpora lutea counts and total implants. However, there were statistically significant differences at 1000 mg/kgBW/day for post-implantation losses, days of gestation, total pups and total live pups with the 1000 mg/kgBW/day group having significantly more postimplantation losses, a longer

gestation period, fewer pups in the litter and fewer live pups in the litter than were seen in the control group.
There were no statistically significant differences across treatment groups for the number of male pups, the number of female pups and the male/female ratio although there was a significant litter size effect for both the number male and number female pups with a fewer number of male pups than female pups appearing in smaller litter sizes.

The number of day 4 viable pups and the ratio of the number of viable pups to the total litter size was significantly different, with the 1000 mg/kgBW/day group having fewer viable pups by day 4 and a smaller viable/total ratio than did the control group. The percentage of post-natal loss was significantly different, with the 1000 mg/kgBW/day having a significantly higher loss than did the control group.

The initial litter weight and average pup weights (defined using the live pup litter weight divided by the total number of live pups on day 0) were significantly different only for the 250 mg/kgBW/day group having a significantly increased litter weight and average pup weight compared to that in the control group after adjusting for litter size. The litter size was also a significant variable for these two endpoints with larger litters having larger litter weights but smaller average pup weights.
For the final litter weight and average pup weights, there was also a significant difference, but it was the 1000 mg/kgBW/day group that was significantly different from the control group with both smaller overall litter weights and smaller average pup weight than in control group. There were no grossly visible external abnormalities observed in the pups. Based on results observed at 1000 mg/kgBW/day in male (hepatic protoporphyrin accumulation, adrenal cortical atrophy, kidney protein droplet nephropathy, testicular seminiferous tubule degeneration with epididymides involvement) and in female rats (periportal vacuolation), the NOAEL (No-Observed-Adverse-Effect-Level) for systemic toxicity of dimethyldimethoxysiIane is 250 mg/kgBW/day. Based on observations at 1000 mg/kgBW/day (an increase in postimplantation loss, an increase in days of gestation, a decrease in live pups, a decrease in the total viable pups/total, a decrease in final litter weight, a decrease in final average pup weight and an increase in the % of post-natal loss), the NOAEL mg/kgBW/day for reproductive and developmental toxicity is 250 mg/kgBW/day (Dow, 2010).

Derivation of Screening Level

The oral study by Dow (2010) was well performed and provides data for the derivation of a reference dose (RfD) for dimethoxydimethylsilane. Inhalation studies in general are preferred when deriving an inhalation reference dose, especially when portal of entry effects are relevant. However, the acute inhalation study provided no information on effects in the lungs and scant data on other organ systems. A Lethal Dose 50 was not calculated because there was only one exposure dose level for dimethoxydimethylsilane. An LD zero (LD0) of 4700 mg/m^3 is likely an overly conservative measurement of acute inhalation toxicity. If the LD0 was considered as a surrogate LD50 an ITSL could be calculated based on Rule 232(1)(f) as follows:

ITSL = LD50/(500x100)
ITSL = 4700mg/m³/(50000) x 1000µg/mg
ITSL = 94 µg/m³ ~ 90 µg/m³ annual averaging time, pursuant to Rule 232(2)(c)

The oral study could be used to derive an ITSL via an oral RfD, derived as follows:
RfD = NOAEL/(UF1xUF2xUF3xUF4) x DAF
RfD = (250mg/kg)/(10x10x10x2) x 0.25
RfD = 0.031 mg/kg

Where NOAEL is 250 mg/kgBW/day
DAF (dosimetric adjustment factor) of $(BW_a/BW_h)^{1/4}$ = 0.25
BW_a = body weight of the female rat at 0.25 kg
BW_h = body weight of human at 70 kg
UF1 is uncertainty factor of 10 for animal to human extrapolation
UF2 is 10 for sensitive individuals
UF3 is 10 for subchronic to chronic
UF4 is 2 for subacute (28days) to subchronic (90 days)

ITSL = RfD x 70kg/20m³ x 1000 µg/mg; pursuant to Rule 232(1)(b)
ITSL = 109 µg/m³ ~100 µg/m³; annual averaging time pursuant to Rule 232(2)(b)

Since the two ITSLs are very similar (90 µg/m³ versus 100 µg/m³), and the inhalation data is likely more relevant to air pollution control and inhalation toxicity, the ITSL based on the LD0 was preferred for derivation of the ITSL.

References

Dow. 2010. Dow Corning Corporation. HES Study Number: 10705- 102.

REACH. Registration, Evaluation, Authorisation and Restriction of Chemicals. 2013. Dimethoxydimethylsilane. Registered Substance of European Chemicals Agency (ECHA). https://echa.europa.eu/registration-dossier/-/registered-dossier/13186/7/3/3