MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for *d*-Limonene (CAS# 5989-27-5)

FROM: Keisha Williams, Air Quality Division

DATE: June 30, 2016

SUBJECT: Screening Level Update for *d*-Limonene

The initial threshold screening level (ITSL) for *d*-limonene is 6,250 µg/m^3 (annual averaging time) based on the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) Rule 336.1229 (2) (b) and 336.1232 (1) (a). The ITSL was originally established with an averaging time set at 24 hours per AQD Rules 232 (2). It is being changed at this time to annual, as allowed per Rule 229 (2), because the original derivation accounted for chronic exposure. Attached is the June 23, 1996 memo describing the derivation of the ITSL value.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

June 23, 1996

TO: File for *d*-Limonene (CAS# 5989-27-5)

FROM: Michael Depa, Toxics Unit, Air Quality Division

SUB JECT: Screening Level Determination

The initial threshold screening level (ITSL) for *d*-limonene is 6,250 µg/m^3 based on a 24 hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: IRIS, RTECS, ACGIH Threshold Limit Values, NIOSH Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, IARC Monographs, CAS Online (1967 - October 28, 1995), National Library of Medicine, Health Effects Assessment Summary Tables, and NTP Status Report. Review of these sources found that EPA has not established an RfC or RID for *d*-limonene. There were no occupational exposure limits for *d*-limonene.

d-Limonene is one of a number of unique compounds that cause male rat specific kidney tumors. These tumors are associated with the accumulation of α_{2u}-globulin in hyaline droplets in the proximal convoluted tubule in the male rat but not the female rat or most notably male and female mice. The EPA (1991) stated, "Since humans appear to be more like other laboratory animals than like the male rat, in this special situation, the male rat is not a good model for assessing human risk." In 1991, the EPA published guidance concerning the use of kidney lesions for assessing human risk:

> 1. Male rat renal tubule tumors arising as a result of a process involving α_{2u}-globulin accumulation do not contribute to the qualitative weight-of-evidence that a chemical poses a human carcinogenic hazard. Such tumors are not included in dose-response extrapolations for the estimation of human carcinogenic risk.
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> 2. If a chemical induces α_{2u} -globulin accumulation in male rats, the associated nephropathy is not used as an endpoint for determining non-carcinogenic hazard. Estimates of non-carcinogenic risk are based on other endpoints.

The EPA (1991) also provided criteria for evaluating chemically induced male rat renal tubule tumors. Three conditions must be met before it can be concluded that the male rat renal tubule tumors are not to be used for carcinogenic risk analysis. These conditions are listed below.

> 1. Increased number and size of hyaline droplets in renal proximal tubule cells of treated rats

2. Accumulation of protein in the hyaline droplets is α_{2u}-globulin

3. Additional aspects of the pathological sequence of lesions associated with α_{2u}-globulin nephropathy are present (e.g. linear mineralization and tubule hyperplasia)

The National Toxicology Program (NTP, 1990) performed a gavage bioassay using *d*-limonene in male and female F344/N rats and B6C3F1 mice. This was before EPA came out with their risk assessment policy on male rat α_{2u}-globulin associated nephropathy. NTP concluded that there was clear evidence of carcinogenic activity in male F344/N rats and no evidence of carcinogenic activity in female F344/N rats or male and female B6C3F1 mice. In their guidance publication, the EPA lists *d*-limonene as positive in male and negative in female rats for evidence of exacerbation of hyaline droplets in renal proximal tubule cells (EPA, 1991). Likewise, there is positive evidence in male rats and negative evidence in female rats for renal α_{2u}-globulin levels (EPA, 1991). Furthermore, in the NTP gavage bioassay mentioned above, there was a dose-related increased incidence of mineralization and epithelial hyperplasia in the male rat. In a 21-day study conducted after the 2-year bioassay, microscopic examination of paraffin-embedded sections of kidney revealed an increased number of intracytoplasmic granules within many of the cells that came from the *d*-limonene dosed rats compared to the vehicle control. The intracytoplasmic granules in vehicle controls and dosed male rats stained positively for α_{2u}-globulin. Quantitation of α_{2u}-globulin showed a significantly increased quantity (mg/ml) of α_{2u}-globulin in dosed male rats compared to vehicle control ($p<0.01$). In the female rats there were no differences in the distribution or amount of the granules between the dosed and vehicle control groups. Since *d*-limonene meets the 3 conditions set forth by the EPA for α_{2u}-globulin associated nephropathy, the kidney tumors and other kidney pathologies elicited in the male rat will not be used in the risk assessment process. Other endpoints will be used to determine an acceptable human exposure limit.

In a human study, eight healthy men, with an average age of 30 (range 23-38) years and an average weight of 75 (range 64-82) kg, were exposed to 10, 225, or 450 mg/m^3 *d*-limonene for 2 hours at 3 different exposure occasions, during light physical exercise on a bicycle (Falk-Filipsson et al., 1993). There were 2 weeks between exposure occasions. The 10 mg/m^3 dose was chosen so that the subjects could smell the solvent and thus not find out what level they were exposed to. The relative uptake of *d*-limonene during 2 hours of exposure at light physical exercise averaged 68% of the amount supplied for the 2 higher concentrations and 63% at the control or 10 mg/m^3 dose level. The absolute uptake increased linearly with exposure concentration. The 4 hour clearance rate was 1.1 L kg^{-1} h^{-1} for the medium exposure and 1.4 L kg^{-1} h^{-1} for the high exposure. The authors stated, “About 1% of the total uptake was eliminated unchanged in the expired air after the end of exposure, while approximately 0.003% was eliminated in the urine. A long half-time in blood was observed in the slow elimination phase, which indicated accumulation in adipose tissues.

The subjects did not experience any irritative symptoms or symptoms related to the central nervous system. The maximum vital capacity lung function test was significantly decreased in the high exposure group by 2% ($p<0.01$) compared to control. Many other lung function tests (e.g. $FEV_{1.0}$, PEF, RV, TLC, mean expiratory flow at 50% VC, and airway resistance [raw]) showed no difference from control. The

authors mentioned that larger group sizes would be necessary for a more adequate assessment of the acute effects of *d*-limonene exposure.

In a subacute range finding study, groups of 5 Wistar rats/sex were fed diets with 0, 250, 1000, or 4000 ppm *d*-limonene for 4 weeks (Jonker et al., 1993). In male rats at the 4000 ppm dose level there were increases in the relative kidney weight and volume of the urine collected in 1 week (statistical analysis not presented). In slightly older male rats given the same dosing regimen (10 weeks old vs. 4 weeks), there were increased number of epithelial cells in the urine in the 4000 ppm group (statistical analysis not presented). Other changes in the male 4000 ppm group were microscopic renal changes consisting of nephrosis and accumulation of proteinaceous droplets in the tubular epithelial cells. Nothing was mentioned about the female dose groups.

In the main study, groups of 10 male and female Wistar rats were fed diets of 0, 500, or 4000 ppm *d*-limonene for 4 weeks (Jonker et al., 1993). The authors stated that the dose level of 500 ppm is about 30 mg/kg. Based on the food intake and average body weight of the 4000 ppm rats the dose was estimated to be about 210 mg/kg. Parameters analyzed in the male rats included: body weight, food intake, water intake, urine volume, urine density, amount of epithelial cells in urine, urine ketones, ALP, bilirubin, and relative and absolute kidney, adrenal and liver weights. Parameters analyzed in the female rats include all of the ones analyzed in the male rat plus ASAT, ALAT, albumin, total protein, and calcium. In the male rat at the 500 ppm dose but not the 4000 ppm dose the urine density was significantly lower than the control group ($p<0.01$). In the male rat the urine epithelial cells were significantly increased at both dose levels compared to controls ($p<0.02$ and 0.002 respectively). The only other finding in the male rat was a decrease in relative adrenal weight at the 500 ppm dose level ($p<0.05$); however, there was no difference at the 4000 ppm dose level. Because there was an increase in urine density and adrenal weight at the 500 ppm level but not at the 4000 ppm level it was deemed that these results were not related to dose. An increase in epithelial cells in the wine was observed at both dose levels; however, these effects are probably related to α_{2u}-globulin associated nephropathy. Therefore, the effects observed in the male rat were not considered in establishing an adverse effect level. The NOAEL in the male rat was determined to be 4000 ppm or about 210 mg/kg. In the female rat the only difference from control rats was an increase in the calcium level in the blood at the 500 ppm level but not the 4000 ppm dose level ($p<0.01$). Because this effect was not seen at the 4000 ppm dose level it was deemed not to be related to dose. The 4000 ppm dose level was determined to be a NOAEL.

In an oral study, groups of 15 to 18 mice (from Schofield and Company; strain unspecified) evenly divided between sexes were exposed via gastric intubation to 0.05 ml (~1200 mg/kg) *d*-limonene once a week for 40 weeks (Field et al., 1965). All mice were denied food for 18 hours before each treatment. All mice were weighed every 2 weeks and the average weight per group was recorded graphically. Sick mice were killed and like those that were found dead, were autopsied. The entire gastrointestinal tract was examined. Segments of the stomach and any other organ showing gross pathological change were analyzed histopathologically. The incidence of animals with tumors was 2/15 for the *d*-limonene treated mice and 0/18 for the control (solvent dosed) mice. A Fisher's Exact Test revealed that the P value was 0.19 and therefore, the dose group incidence of animals with tumors was not significantly different from the control group incidence. The authors stated that the growth curves were similar. No other

information was given about the effects of *d*-limonene treatment. The NOAEL for this study was determined to be 1200 mg/kg.

In a subchronic oral study in dogs, groups of 15 male and female pure-bred beagles were dosed by gavage with 0, 100, or 1000 mg *d*-limonene/kg/day for 180 consecutive days (Webb et al., 1990). Extensive hematological and clinical chemistry analysis were performed 2 weeks prior to testing and 1, 3, and 6 months into the study. Twenty four hour urine samples were collected at 2 weeks pre-study and at 6 months. On completion of the study an autopsy/histology analysis was performed. All the major organs and tissues were analyzed. There was no effect on body weight but the absolute and relative kidney weights were increased in female dogs given 1000 mg/kg ($P<0.05$). Relative kidney weight was increased in the male dogs at 1000 mg/kg ($P<0.05$). The only clinically significant results were an increase in serum cholesterol (35%) and serum alkaline phosphotase levels (two-fold increase) in dogs (both male and female) given 1000 mg/kg (significance level not given). No histopathological differences were found in any of the dogs. A LOAEL of 1000 mg/kg was identified based on increased serum cholesterol and alkaline phosphotase and increased relative kidney weight in both males and females. A NOAEL of 100 mg/kg was also identified.

In an acute study, groups of 5 male and female F344/N rats and B6C3F1 mice were dosed by gavage with 0, 413, 825, 1650, 3300, or 6600 mg/kg *d*-limonene 5 days/week over 16 days (total of 12 doses) (NTP, 1990). Necropsy was performed on all animals and histologic exams were performed on 6 mice and 7 rats from survivors of the highest dose groups. All rats that received 6600 mg/kg and 5/5 males and 3/5 females that received 3300 mg/kg *d*-limonene died within the first 2 days. The final mean body weight of the male rats that received 1650 mg/kg was 10% lower than that of the vehicle controls. The final mean body weight of female rats that received 3300 mg/kg was 8% lower than that of the vehicle controls. No compound-related clinical signs were observed in rats that received doses of 1650 mg/kg or lower. No compound-related lesions were observed/reported. A LOAEL of 1650 mg/kg in male rats was identified based on decreased body weight. The corresponding NOAEL for male rats was 825 mg/kg. The NOAEL in female rats was 1650 mg/kg.

In the mice, all but one of 20 mice that received 3300 or 6600 mg/kg died within 3 days. No compound related clinical signs were observed in mice that received 1650 mg/kg and lived to the end of the studies. No compound related histopathologic lesions were observed in the mice. The NOAEL in male and female mice was 1650 mg/kg; decreased survival was observed at 3300 mg/kg (FEL).

In a subchronic study, groups of 10 male and female F344/N rats were dosed by gavage with 0, 150, 300, 600, 1200, or 2400 mg/kg *d*-limonene for 5 days/week for 13 weeks (NTP, 1990). At the same time, groups of 10 male and female B6C3F1 mice were dosed by gavage with 0, 125, 250, 1000, or 2000 mg/kg *d*-limonene for 5 days/week for 13 weeks. Necropsy was performed on all animals. Histologic exams were performed on all vehicle control and high dose animals and all female rats in the 1200 mg/kg group. Kidneys were examined for all male rats. Five of 10 males and 9/10 female rats that received 2400 mg/kg died during week 1 of dosing. The final mean body weights of male rats that received 600, 1200, or 2400 mg/kg were 6%, 12%, or 23% (respectively) lower than that of the vehicle controls. The final mean body weight of the female rats that received 2400 mg/kg and lived to the end of the study

was 11% lower than the mean of the vehicle controls. Rough hair coats, lethargy, and excessive lacrimation were observed for rats that received 1200 or 2400 mg/kg. Nephropathy was identified in all groups of male rats, but there was a dose-related increased severity of the lesion in dosed groups. The nephropathy was characterized by degeneration of epithelium in the convoluted tubules, granular casts within tubular lumens, primarily in the outer stripe of the outer medulla, and regeneration of the tubular epithelium. Hyaline droplets were observed in the epithelium of proximal convoluted tubules in all groups of male rats, including vehicle controls. Otherwise, no histopathological results were reported. A LOAEL of 1200 mg/kg was identified in male and female rats based on decreased body weight (difference from control weight> 10%; males only), rough hair coats, lethargy and excessive lacrimation. A NOAEL for male and female rats is 600 mg/kg. Male kidney pathology was not considered an adverse effect (see EPA, 1991 summarized above).

In the mice: 1/10 males and 2/10 females that received 2000 mg/kg and 1/10 females that received 500 mg/kg died before the end of the studies. Clinical signs of rough hair coats and decreased activity were observed at the two highest doses (1000 and 2000 mg/kg) for both male and female mice. The final mean body weights of mice that received 1000 or 2000 mg/kg were 10% lower than that of the vehicle controls for males and 2% lower for females. No histo-pathological results were reported. Based on decreased body weight in males, and rough hair coats and decreased activity in males and females the LOAEL in male mice was 1000 mg/kg and the NOAEL was 500 mg/kg.

In a chronic gavage study (also mentioned above), groups of 50 male F344/N rats were dosed by gavage with 0, 75, or 150 mg/kg *d*-limonene 5 days per week, whereas female rats were dosed with 0, 300, or 600 mg/kg *d*-limonene 5 days per week (NTP, 1990). In the same dose schedule, male B6C3F1 mice were dosed with 0, 250, or 500 mg/kg *d*-limonene, whereas female mice were dosed with 0, 500, or 1000 mg/kg *d*-limonene. Necropsy and extensive histopathology were performed on all animals. No compound related clinical signs were observed. Body weights were within 10% of vehicle control. The survival of the female rat high dose group (600 mg/kg) was significantly lower ($P<0.006$) than controls. Cataracts were observed at increased incidences in high dose male and dosed female rats (male: vehicle control, 1/50; low dose, 3/50; high dose, 27/50; female: 0/50; 5/50; 20/50). Retinal degeneration was observed in dosed male and female rats (male: 0/50; 7/50; 37/50; female: 0/50; 21/50; 28/50). NTP stated that these changes are not believed to be related to the administration of *d*-limonene but rather to the proximity of animal cages to the light source in the animal room. Male rat survival was significantly greater at 150 mg/kg; this dose was considered a NOAEL for male rats. No other dose related effects (except the kidney lesions) were seen in the male rats. A LOAEL of 600 mg/kg was identified in female rats based on decreased survival. The NOAEL in female rats was 300 mg/kg.

In the mice, mean body weights of dosed and vehicle control male mice were similar throughout the studies. Mean body weights of high dose female mice were 5-15% lower than those of the vehicle controls after week 28, but were normal by the end of the study. No compound related clinical signs were observed during the 2-year studies. Survival of the low dose male mice was significantly lower than that of the vehicle controls ($P = 0.048$). No statistical difference in survival was noted in the female or high dose male groups. The decreased survival of the low dose male mice group was not considered compound related because the high dose male group had greater survival than the vehicle controls.

Hepatocytes containing three or more nuclei and cytomegaly occurred at statistically increased incidences in high dose male mice (multinucleated cells - male: vehicle control, 8/49; low dose, 4/3 6; high dose, 32/50; female: none observed; cytomegaly - male: 23/49; 11/36; 38/50; female: none observed). The high dose (500 mg/kg) in the male mice was considered a LOAEL due to the increased incidence of multinucleatcd hepatocytes and hepatocellular cytomegaly. A NOAEL of 250 mg/kg was identified in the male mice. A NOAEL of 1000 mg/kg (highest dose tested) was identified in the female mice.

In another subchronic oral dose study, groups of 10 male Fischer 344 rats were dosed with 0, 2, 5, 10, 30, or 75 mg/kg *d*-limonene (in corn oil) for 91 days (Webb, 1989). There was no difference between control and dosed rats in body weight gain, feed consumption or absolute organ weights. Relative kidney and liver weights were significantly increased ($p<0.01$ and 0.05, respectively) at a dose of 75 mg/kg. No histopathological changes were observed in the liver. The accumulation of hyaline droplets in the cytoplasm in epithelial cells of the proximal convoluted tubule was significantly increased at the 10, 30 and 75 mg/kg dose levels ($p<0.05$, 0.01, 0.001, respectively). The authors identified a NOEL of 5 mg/kg. However, according to EPA the α_{2u}-globulin associated nephropathy is not used as an endpoint for determining non-carcinogenic hazard. Furthermore, the appropriateness of designating the effects seen at 75 mg/kg as the LOAEL based increased relative liver weight was questioned. No histopathological changes accompanied the 6% increased relative liver weight ($p<0.05$) at the 75 mg/kg dose. Given that there were no significant body weight changes at this dose and that no adverse effects or organ weight changes were seen at 600 mg/kg in a 91 day gavage study with male F344/N rats (NTP, 1990; see above) the 75 mg/kg dose was deemed a NOAEL.

Table 1. Summary of Effects Levels for *d*-Limonene

Reference	Study Type and Dose Levels	Effect Levels
Falk-Philipsson et al., 1993	Acute (2 hr), inhalation, human; dose levels = 10, 225, or 450 mg/m^3	human - LOAEL = 450 mg/m^3 - based on decreased maximum vital capacity, NOAEL = 225 mg/ m^3
NTP, 1990	Acute (16 days), oral, rats and mice; dose levels = 0, 413, 825, 1650, 3300, or 6600 mg/kg	male rats - LOAEL = 1650 mg/kg based on decreased body weight; NOAEL = 825 mg/kg female rats - LOAEL = 3300 increased mortality, NOAEL = 1650 mg/kg male and female mice - FEL = 3300 mg/kg based on decreased survival, NOAEL = 1650 mg/kg
Jonker et al., 1993	Subacute (4 weeks), feed, male and female rats; dosage levels = 0, 250, 1000, and 4000 mg/kg and 0, 500, and 4000 mg/kg	male rats - NOAEL = 4000 ppm (~ 210 mg/kg) female rats - NOAEL = 4000 ppm (~ 266 mg/kg)
NTP, 1990	Subchronic (90 days), oral, rats; dose levels = 0, 150, 300, 600, 1200, or 2400 mg/kg	male and female - LOAEL = 1200 mg/kg based on decreased body weight, rough hair coats, lethargy and excessive lacrimation, NOAEL = 600 mg/kg
NTP, 1990	Subchronic (90 days), oral, mice; dose levels = 0, 125, 250, 1000, or 2000 mg/kg	male and female - LOAEL = 1000 mg/kg based on decreased body weight (in males only) and rough hair coats and decreased activity, NOAEL 500 mg/kg
Webb et al., 1990	Subchronic (180 days), oral, dogs; male and female dosage levels = 0, 100, 1000 mg/kg	male dogs - LOAEL = 1000 mg/kg based on increased relative kidney weights and increased serum cholesterol and alkaline phosphotase levels, NOAEL = 100 mg/kg female dogs – LOAEL= 1000 mg/kg based on increased relative and absolute kidney weights and increased cholesterol and alkaline phosphotase, NOAEL=100 mg/kg
Webb et al., 1989	Subchronic (91 days), oral, male rats; dosage levels = 0, 2, 5, 10, 30 or 75 mg/kg	male rat – NOAEL= 75 mg/kg
NTP, 1990	Chronic (2 years), oral, rats; male dosage levels = 0, 75, or 150 mg/kg; female dosage levels = 0, 300, or 600 mg/kg	male rats - NOAEL = 150 mg/kg female rats - FEL = 600 mg/kg based on decreased survival, NOAEL = 300 mg/kg
NTP, 1990	Chronic (2 years), oral, mice; male dosage levels = 0, 250, or 500 mg/kg; female dosage levels = 0, 500, 1000 mg/kg	male mice - LOAEL = 500 mg/kg based on increased incidence of multinucleated hepatocytes and hepatocellular cytomegaly, NOAEE = 250 mg/kg (used to derive ITSL) female mice - NOAEE = 1000 mg/kg

When evaluating the toxicological data on *d*-limonene, several factors were considered including the species tested, the route of dosing, the duration, and the thoroughness of the toxicological examination. The only human study available was an acute inhalation study. Two factors make this a very valuable study: the fact that it is in humans and the route of exposure is by inhalation. However, the short duration and lack of clinical pathology tests (e.g. blood and urine tests) are deficiencies in this study. The subchronic dog study (Webb et al., 1989) was deemed inappropriate to use to develop the ITSL because it was of shorter duration than the chronic rat study (NTP, 1990) and had a NOAEL at a higher dose level than the rat study. The chronic study performed in rats and mice (NTP, 1990) was considered in developing the final ITSE. There were several effect levels to consider. A frank effect level (decreased survival) was observed in the female rats at 600 mg/kg (the highest dose tested). The NOAEL in female rats was 300 mg/kg. In male mice there was increased incidence of multinucleated hepatocytes and hepaocellular cytomegaly observed at 500 mg/kg (LOAEL). The lowest NOAEL is 250 mg/kg in male mouse. The chronic study in the male mouse (NTP, 1990) was considered more appropriate to use than the acute human study because of the longer duration and the complete toxicological analysis performed. The NOAEL in the male mouse was chosen for the development of the screening level according to EPA methodology (EPA, 1994). The RfD was developed first, then the ITSL was derived.

$$RfD = \frac{NOAEL}{UF_1 x\, UF_2}\, x \frac{5\ days}{7\ days}$$

Where, UF_1 is 10 to account for sensitive subpopulations
UF_2 is 10 for animal to human extrapolation

$$RfD = \frac{250 \frac{mg}{kg}}{100}\, x \frac{5}{7}$$

$$RfD = 1.78\ \frac{mg}{kg}\ per\ day$$

$$ITSL = RfD\, x \frac{70\ kg}{20 m^3}$$

$$ITSL = 1.78 \frac{mg}{kg} per\ day\, x \frac{70\ kg}{20 m^3}$$

ITSL = 6,250 µg/m^3 (based on a 24 hour averaging time)

The ITSL for *d*-limonene is 6,250 µg/m^3 based on a 24 hour averaging time.

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