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2,2,4-Trimethyl-1,3-pentanediol monoisobutyrate (TPM, Texanol™, NX 795, or UCAR™ Filmer IBT)

CAS Registry Number: 25265-77-4

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Revision History

Original Development Support Document (DSD) posted as final on April 15, 2008.

Revised DSD September 14, 2015: the odor-based value was withdrawn because 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate does not have a pungent, disagreeable odor (TCEQ 2015).

Table of Contents

List of Tables

List of Figures

Chapter 1 Summary Tables

A summary of health- and welfare-based values from an acute and chronic evaluation of 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate (TPM) can be found in Table 1. Summary information on the physical/chemical parameters of TPM can be found in Table 2.

Table 1. Health- and Welfare-Based Values

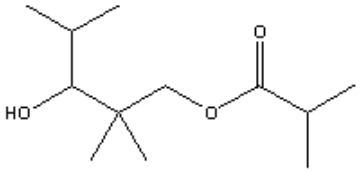
Short-Term Values	**Concentrations VOC[a]**	**Concentrations PM[b]**	**Notes**
acute ReV (HQ = 1.0)	3,400 µg/m^3 (380 ppb)	13,000 µg/m^3	**Critical Effect(s):** Freestanding NOAEL, no adverse effects observed
^{acute}ESL (HQ = 0.3)	1,000 µg/m^3 (110 ppb) **Short-Term ESL for VOC Air Permit Reviews**	MUST MEET 24 h PM_{10} NAAQS (150 µg/m^3) **Short-Term ESL for PM Air Permit Reviews**	**Critical Effect(s):** Same as above
$^{acute}ESL_{odor}$	---	---	Mild odor
$^{acute}ESL_{veg}$	---	---	Concentrations tested did not produce vegetative effects
Short-Term Values	**Concentrations VOC[a]**	**Concentrations PM[b]**	**Notes**
chronic ReV (HQ = 1.0)	1,300 µg/m^3 (150 ppb)	5,400 µg/m^3	**Critical Effect:** Freestanding NOAEL, no adverse effects observed. Annual PM_{10} NAAQS was revoked.
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	390 µg/m^3 (44 ppb) **Long-Term ESL for VOC Air Permit Reviews**	See Section 4.1.4.2	**Critical Effect(s):** Same as above
$^{chronic}ESL_{linear(c)}$ $^{chronic}ESL_{nonlinear(c)}$	---	---	No data found
$^{chronic}ESL_{veg}$	---	---	No data found

[a]Refers to volatile organic compound (VOC) values that are relevant under Section 3.1.2

[b]Refers to particulate matter (PM) values that are relevant under Section 3.1.2

Abbreviations: **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; **NAAQS**, National Ambient Air Quality Standards; **NOAEL**, No-Observed Adverse Effect Level; **ReV**, Reference Value; **ESL**, Effects Screening Level; $^{\textbf{acute}}\textbf{ESL}$, acute health-based (HB) ESL; $^{\textbf{acute}}\textbf{ESL}_{\textbf{odor}}$, acute odor-based ESL; $^{\textbf{acute}}\textbf{ESL}_{\textbf{veg}}$, acute vegetation-based ESL; $^{\textbf{chronic}}\textbf{ESL}_{\textbf{nonlinear(nc)}}$, chronic HB ESL for nonlinear dose-response (DR) noncancer effects; $^{\textbf{chronic}}\textbf{ESL}_{\textbf{linear(c)}}$, chronic HB ESL for linear DR cancer effect; $^{\textbf{chronic}}\textbf{ESL}_{\textbf{nonlinear(c)}}$, chronic HB ESL for nonlinear DR cancer effect; $^{\textbf{chronic}}\textbf{ESL}_{\textbf{veg}}$, chronic vegetation-based ESL; and **HQ**, hazard quotient.

Table 2. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	$C_{12}H_{24}O_3$	IUCLID 2000
Chemical Structure		Chemfinder 2004
Molecular Weight	216.32	Chemfinder 2004; Eastman 2005a
Physical State	Liquid	Eastman 2005a
Color	Colorless	Eastman 2005a
Odor	Mild	Eastman 2005a
CAS Registry Number	25265-77-4	IUCLID 2000; Eastman 2005a
Synonyms	2,2,4-trimethyl-1,3-pentanediol monoisobutyrate; propanoic acid, 2-methyl-, monoester with 2,2,4-trimethyl-1,3-pentanediol; 2,2,4-trimethyl-1,3-pentanediol mono(2-methylpropanoate); NX 795; UCAR™ Filmer IBT; TPM; TMPD-MIB	Eastman 2005a; IUCLID 2000; As used in Published Literature
Solubility in water	0.1% @ 20ºC	Eastman 2005a
Log K_{ow} or P_{ow}	P_{ow} = 3.47 @ 25ºC	IUCLID 2000
Vapor Pressure	0.01 mmHg @ 20ºC 0.013 mmHg @ 25ºC 0.25 mmHg @ 55ºC	Eastman 2005a; IUCLID 2000; NIOSH 1994
Vapor Density (air = 1)	7.5	Eastman 2005a
Density	0.95 g/cm^3 @ 20ºC	Eastman 2005a; IUCLID 2000
Melting Point	-50ºC	IUCLID 2000; Eastman 2005a
Boiling Point	254 – 260.5ºC	Eastman 2005a
Conversion Factors (VOC only)	1 µg/m^3 = 0.11 ppb @ 25ºC 1 ppb = 8.85 µg/m^3 @ 25ºC	CDC

Chapter 2 Major Uses or Sources

TPM is manufactured under the trade names Texanol™ Ester Alcohol, NX 795, and UCAR™ Filmer IBT. TPM is a solvent used mainly as a coalescent for latex paints. Other applications include: architectural and industrial maintenance, chemical intermediate for synthesis of ester derivatives for plasticizers, electrodeposition primers and coatings, floor polishes, high-bake enamels and other solvent-borne coatings, lithographic and letterpress oil-based inks, recovery solvent in drilling muds and ore flotation processes, solvents for nail polish, solvents for cosmetics and personal care, and wood preservatives (Eastman 2005b). Acute Evaluation

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

3.1.1 Physical/Chemical Properties and Key Studies

TPM is a colorless liquid with a low vapor pressure and low water solubility. According to the Cramer classification scheme, the chemical structure is an open chain aliphatic with functional groups which are not associated with enhanced toxicity (ECB 2007). The Cramer classification scheme classifies chemical toxicity based on chemical structure and known pathways for metabolic activation and deactivation (Cramer 1978). This classification scheme was originally developed for oral toxicity and can contribute to the weight of evidence to indicate whether the chemical structure presents a potential concern for toxicity. Under this scheme, TPM is classified as a Class I (low) chemical (ECB 2007). Class I chemicals have a simple chemical structure, generally with known metabolic pathways which produce innocuous end points (Cramer 1978). The main chemical and physical properties are summarized in Table 2.

Only one acute inhalation toxicity study could be identified for TPM, which was conducted by the Eastman Kodak Company in 1960 (Morison 1960). However, this was an unpublished study, and the details are not available. The study notes state that animals were sacrificed for pathology, and no clinical symptoms occurred (clinical or pathological) in two sets of three rats after 6 hs of exposure to 3,550 or 8,730 mg/m^3 of TPM. In this study no adverse health effects occurred from high dose inhalation exposure, which indicates that point of entry (POE) effects would not be expected to occur. In addition, due to the chemical structure, low vapor pressure, and low water solubility of TPM, the TS would not expect to see POE effects when inhaled. This inhalation study supports the conclusion that a route-to-route extrapolation from oral gavage to inhalation is appropriate. Therefore, a 15-day repeated dose oral gavage study was used to derive the TPM health-based ^{acute}ESL (O'Donoghue 1984). In this study, no first-pass liver effects were observed. A freestanding no-observed-adverse-effect level (NOAEL), meaning no dose was administered at which adverse effects were observed, was determined from the available acute data. Since no adverse effects were observed, a dose-response relationship associated with toxic endpoints for TPM could not be determined. The conclusions of this study correspond to conclusions of a well-designed subchronic, oral, repeated dose and reproductive/developmental study (Faber and Hosenfeld 1992). TPM did not produce any reproductive/developmental effects.

In the key study (O'Donoghue 1984), three groups of ten rats (five males, five females) were exposed to 0, 100 or 1,000 mg/kg/day TPM over a 15 day time period. Dosing actually occurred for 11 days, as it was not carried out over weekends. Control groups received distilled water. The liver and kidney are possible target organs in this study, due to the increased liver weight and hyaline droplet accumulation in the kidney. The 1,000 mg/kg/day treatment group experienced a slight increase in absolute and relative liver weights. According to the ESL Guidelines (Table E-1, TCEQ 2006a) this effect is considered a mild effect severity level, and could be considered a NOAEL or lowest-observed-adverse-effect level (LOAEL). The TS considers this a NOAEL, because the serum enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were not measured at concentrations significantly different from the 100 and 1,000 mg/kg/day groups when compared to controls. Elevated AST and ALT levels are an indication of hepatocellular injury (Klaassen 2001, Giboney 2005). Since there was no change in these levels between the treated groups and controls, it suggests that hepatocellular injury did not occur. All treated males exhibited minimal to minor hyalin droplet degeneration in the kidneys. Hyalin droplet formation has questionable relevance to humans, as male rats, treated or untreated, are prone to hyalin droplet accumulation. Based on the observed effects, which are mild and do not appear to be toxicologically adverse, a NOAEL of 1,000 mg/kg/day was determined for both male and female rats in this study.

3.1.2 Mode-of-Action (MOA) Analysis and Dose Metric

Toxicokinetic studies of TPM (2,2,4-trimethyl-1,3-pentanediol monoisobutyrate) have not yet been conducted. However, it is closely related to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TXIB), and therefore a proposed metabolic pathway for Texanol™ has been developed based on oral studies of TXIB (Figure 1) (Nielsen et al. 1997). The potential metabolites include diols and carboxylate compounds and their metabolites, which are hydrophilic and would be expected to be eliminated through urine. Cytochrome P450 would not likely oxidize the parent chemical significantly because the C2 and C4 carbon atoms are protected by the methyl (CH_3) groups (Nielsen et al. 1997).

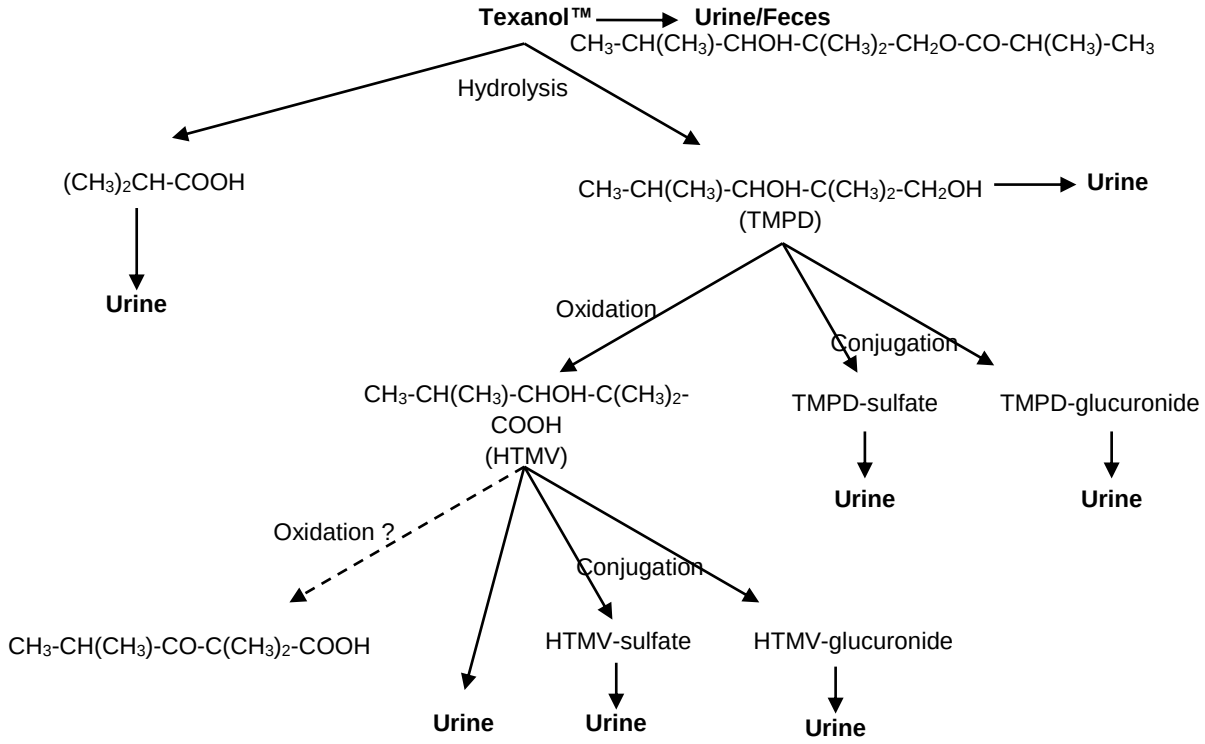


Figure 1 Proposed metabolic pathway for Texanol™.
Solid lines are known major metabolic pathways; broken line is a hypothetical metabolic pathway. Figure is adapted from Fig. 1 in Nielsen et al. 1997.

Data on the exposure dose of the parent chemical is available for the key study (O'Donoghue 1984). Since the MOA of TPM is not fully understood, and data on other more specific dose metrics is not available (e.g., blood concentration of parent chemical, area under blood concentration curve of parent chemical, or putative metabolite concentrations in blood or target tissue), exposure dose of parent chemical converted to an inhalation equivalent using route-to-route extrapolation will be used as the default dose metric.

TPM can be emitted as a vapor or a mist as outlined by the TCEQ Air Permit Division (TCEQ 2006b). TPM is treated as a vapor (volatile organic compound (VOC)) when the process temperatures are such that the vapor pressure is greater than 0.1 mmHg. TPM is treated as a mist (particulate matter (PM)) when the process temperatures are such that the vapor pressure is less than 0.1 mmHg. A mist is considered PM for both air permitting and inhalation dosimetry purposes. Acute ReVs and ESLs were derived for TPM as outlined in the following sections based on whether TPM was considered a VOC or PM.

3.1.3 Point of Departures (PODs) for the Key Study and Dosimetric Adjustments

The NOAEL of 1,000 mg/kg was converted to an inhalation equivalent using route-to-route extrapolation (Appendices A-C) since data needed for a physiologically-based pharmacokinetic model or other dosimetric model were not available for TPM. As data were not available on the body weight or species of the rats tested, a generic rat body weight (USEPA 1988) and inhalation rate (USEPA 1988) were used for the conversion to an inhalation equivalent. The calculated inhalation equivalent POD_{ADJ} used was 1,035.4 mg/m^3.

3.1.3.1 VOC

The acute inhalation study conducted by the Eastman Kodak Company (Morison 1960) indicates that TPM does not have POE effects. However, there is not sufficient information available to classify TPM as a category 1, 2 or 3 vapor for animal to human dosimetric adjustments. Therefore, no animal to human dosimetric adjustments were used for the acute VOC evaluation of TPM. In lieu of a POD_{HEC}, the POD_{ADJ} from Section 3.1.3 was applied, resulting in a subacute POD_{ADJ} for TPM as a VOC of 1,035,400 $\mu g/m^3$.

3.1.3.2 PM

The CIIT Centers for Health Research (CIIT) and National Institute for Public Health and the Environment (RIVM) 2002 multiple path particle dosimetry model (MPPD) v 2.0 program (CIIT and RIVM 2002) was used to calculate the deposition fraction for TPM in the target respiratory region. Parameters necessary for this program are particle diameter, particle density, chemical concentration, and species. According to Appendix H of USEPA 1994, a mist has a diameter of <1 – 20 µm. Therefore, the median diameter of a mist would be 10 µm, which is also considered the respirable range of PM. The target region for TPM was considered to be the total particle distribution for the head, tracheobronchial, and pulmonary regions. Once total particle distribution was determined (Appendix B), the Regional Deposition Dose Ratio (RDDR) was calculated (RDDR = 1.2257). The RDDR was then used to dosimetrically adjust from an animal to human POD. The subacute POD_{HEC} for TPM as PM = 1,269,300 $\mu g/m^3$.

3.1.4 Adjustments to the POD_{ADJ} and POD_{HEC}

3.1.4.1 VOC

A ReV was calculated from the subacute POD_{ADJ} using an interspecies uncertainty factor (UF) of 10, an intraspecies UF of 10, and a database UF of 3 (total UF = 300). An interspecies UF of 10 was used because there was not sufficient information available to dosimetrically adjust the POD. An intraspecies UF of 10 was used to account for any variability within the human population. Although only the minimum database was met, a database UF of 3 was used because the acute inhalation study demonstrated no point of entry effects, and the subacute study results are consistent with those of the well designed, high quality subchronic study.

When calculating, no numbers were rounded between equations until the ReV was calculated. Once the ReV was calculated, it was rounded to the least number of significant figures of measured values used in the equations (2 significant figures for this evaluation). The rounded

ReV was then used to calculate the ESL, and the ESL subsequently rounded. The acute ReV is 3,400 µg/m^3 (380 ppb), and the short-term ESL is 1,000 µg/m^3 (110 ppb) (Table 3).

3.1.4.2 PM

A ReV was calculated using an interspecies UF of 3, an intraspecies UF of 10, and a database UF of 3 (total UF = 100). An interspecies UF of 3 was used because the MPPD program accounts for toxicokinetic differences and limits uncertainty between rat and human extrapolation. An intraspecies UF of 10 was used to account for any variability within the human population. Although only the minimum database was met, a database UF of 3 was used because the acute inhalation study demonstrated no point of entry effects, and the subacute study results are consistent with those of the well designed, high quality subchronic study.

When calculating, no numbers were rounded between equations until the ReV was calculated. Once the ReV was calculated, it was rounded to the least number of significant figures of measured values used in the equations (2 significant figures for this evaluation). The rounded ReV was then used to calculate the ESL, and the ESL subsequently rounded. The acute ReV is 13,000 µg/m^3, and the short-term ESL is 3,900 µg/m^3 (Table 3). Since TPM is being treated as a mist (PM_{10}) and the derived short-term ESL value is much higher than the PM_{10} National Ambient Air Quality Standards (NAAQS), the short-term ESL for air permit evaluations defaults to the 24 h PM_{10} NAAQS of 150 µg/m^3 (Table 1).

3.1.5 Comparison of ^{acute}ESL to Generic ESL

When a subacute study is used to derive a 1-hr ^{acute}ESL, Section 3.2.3 of the ESL guidelines (TCEQ 2006a) requires a generic ESL be derived using approaches in Section 3.6 for comparison to ensure the derived value is not overly conservative. Ideally, the Threshold of Concern (TOC) approach utilizes the lowest reported inhaled concentrations at which fifty percent of the study specimens die after exposure (LC_{50}). However, specific LC_{50} data were not identified for TPM. When a route-to-route extrapolation is appropriate (as discussed for TPM in Section 3.1.1) LD_{50} data, the dose at which fifty percent of the study specimens die after exposure, may be used. Therefore, LD_{50} oral and intraperitoneal injection (i.p.) values were used to develop the generic ESL using the TOC approach, which is described in Section 3.6.2.3 of the ESL guidelines (TCEQ 2006a). The following acute toxicity data were reported for TPM:

Table 3 Acute toxicity data available for TPM

LD50 (mg/kg)	Animal	Reference	TOC Generic ESL
6,517	Rat (oral)	Carpenter et al. 1974	1,000 µg/m^3
3200 – 6400	Rat (oral)	Morison 1960	1,000 µg/m^3
800 – 1600	Rat (i.p.)	Morison 1960	125 µg/m^3
1600 – 3200 (10% in corn oil)	Rat (oral)	Morison 1960	125 µg/m^3
1600 – 3200 (10% in corn oil)	Rat (i.p.)	Morison 1960	125 µg/m^3
1600 – 3200 (10% in corn oil)	Mouse (oral)	Morison 1960	125 µg/m^3
1600 – 3200 (10% in corn oil)	Mouse (i.p.)	Morison 1960	125 µg/m^3

These LD_{50} values were used to assign TPM to the Categories defined in Table 3-3 of the ESL guidelines (TCEQ 2006a). According to the ESL guidelines (TCEQ 2006a), the TS conservatively chooses the lowest toxicity category indicated by the acute toxicity data. TPM was most conservatively classified in Category 4, which includes LD_{50} values between 300 and 2,000 mg/kg. The generic ESL for Category 4 is 125 µg/m^3. The ESL developed using the TOC approach (125 µg/m^3), a conservative default procedure, is less than the ESL developed using the subacute study (1,000 µg/m^3), which provides confidence that the derived value is not overly conservative.

Table 4. Derivation of the Acute ReV and ^{acute}ESL

Parameter	**Summary**	
Study	Repeat dose – 15 days (O'Donoghue 1984)	
Study population	5 male; 5 female rats per exposure group (strain unknown)	
Study quality	Unknown	
Exposure Methods	Gavage once/day for 11 days @ 0, 100 and 1,000 mg/kg	
Critical Effects	Freestanding NOAEL, no adverse effects observed	
POD (original study)	1,000 mg/kg (NOAEL)	
Exposure Duration	One dose/day for 11 days	
POD_{ADJ} (Extrapolation to inhalation exposure)	1,035.4 mg/m^3	
POD_{ADJ} or POD_{HEC} Dosimetry adjustment from animal concentration to HEC	VOC POD_{ADJ} 1,035,400 µg/m^3	PM POD_{HEC} 1,269,300 µg/m^3 (mist with systemic effects, RDDR = 1.22)
Total uncertainty factors (UFs)	VOC 300	PM 100
Interspecies UF	10	3
Intraspecies UF	10	10
LOAEL UF	NA	NA
Incomplete Database UF	3	3
Database Quality	Minimum	Minimum
Acute ReV (HQ = 1)	3,400 µg/m^3 (380 ppb)	13,000 µg/m^3
Short-term ESL (HQ = 0.3)	1,000 µg/m^3 (110 ppb)	Must meet 24 h PM_{10} NAAQS (150 µg/m^3)

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

One odor paper, Ziemer et al. 2000, which met the TS guideline criteria (TCEQ 2006a) was identified. Based on this study, TPM has a 50% odor detection threshold of 65 ppb. However, TPM has a mild odor so an $^{acute}ESL_{odor}$ was not derived (TCEQ 2015).

3.2.2 Vegetation Effects

One terrestrial plant toxicity study conducted by Eastman Chemical Company was identified (Ziegler 1985). Eighty seeds per plant species (radish, lettuce and ryegrass) were dispersed between four growth pouches per species (twenty seeds per pouch) for a total of twelve pouches. The seeds were exposed to 20 mL of TPM at a concentration of 95 mg/L (100 µL/L) and allowed to grow for seven days. Endpoints of growth inhibition were plant height, root length and germination. No effect was observed in the treated versus control groups. Since the TS sets the $^{acute}ESL_{veg}$ at the threshold of effect, and no effect was observed, an $^{acute}ESL_{veg}$ was not developed for TPM.

Short-Term Values

This acute evaluation resulted in the derivation of the following acute values:

TPM treated as a VOC:

- acute ReV = 3,400 µg/m^3 (380 ppb)
- ^{acute}ESL = 1,000 µg/m^3 (110 ppb)

TPM treated as PM:

- acute ReV = 13,000 µg/m^3
- ^{acute}ESL = Must meet PM_{10} NAAQS of 150 µg/m^3

The short-term ESLs for air permit evaluations are as follows: when treated as a VOC = 1,000 µg/m^3, when treated as PM = Must meet PM_{10} NAAQS of 150 µg/m^3 (Table 1).

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties and Key Studies

Physical/chemical properties are discussed in Section 3.1.1.

A subchronic repeated dose and reproductive/developmental oral gavage study was used to derive the TPM health-based ^{chronic}ESL (Faber and Hosenfeld 1992). In this study, no first-pass liver effects were observed, and as stated in Section 3.1.1, route-to-route extrapolation from gavage to inhalation is acceptable for this chemical. The results of this study are consistent with results from the subacute study in Section 3.1.1, with the same free-standing NOAEL, which provides supporting evidence that effects from exposure to TPM will not change with increased exposure duration.

In the key study (Faber and Hosenfeld 1992), four groups of twenty-four rats (twelve males, twelve females) were exposed to 0, 100, 300 or 1,000 mg/kg/day TPM via repeated dose gavage for 40-51 days. Control groups received distilled water. All treatment groups experienced statistically significantly increased mean liver weights (absolute and relative) when compared to controls. In the 300 and 1,000 mg/kg/day doses, both male and female rats had minimal

centrilobular hepatocytomegaly (enlargement of hepatocytes surrounding the central vein). According to Table E-1 in the ESL Guidelines Table E-1, this is considered a mild effect severity level, and could be considered a NOAEL or LOAEL (TCEQ 2006a). The TS considers this a NOAEL because the serum enzymes AST and ALT were measured at concentrations that were significantly lower in the 100, 300 and 1,000 mg/kg/day groups as compared to controls. Elevated AST and ALT levels are an indication of hepatocellular injury (Klaassen 2001, Giboney 2005); since these levels are lower in the treated groups it suggests that hepatocellular injury has not occurred. In the 1,000 mg/kg/day male rats, kidney weights were statistically significantly increased in the treated groups as compared to the control groups. In the 300 and 1,000 mg/kg/day male rats, histopathological changes in the kidney were also observed (accumulation of hyalin droplets). The authors concluded that these liver changes were due to increased metabolic activity resulting from administration of TPM, rather than from a toxicological adverse effect. The hyalin droplets in the kidneys are not considered a significant adverse effect, as they are suggestive of hydrocarbon nephropathy, which is a lesion unique to male rats (Faber and Hosenfeld 1992). Since all observed effects are considered mild and do not appear to be toxicologically adverse, it was determined that the NOAEL is 1,000 mg/kg/day.

4.1.2 MOA Analysis and Dose Metric

The MOA and dose metric are discussed in Section 3.1.2. Since no dose response is available for TPM to determine linearity, and there is no evidence to suggest a linear MOA, the default nonlinear noncarcinogenic approach as outlined by the ESL guidelines (TCEQ 2006a) was used.

As discussed in Section 3.1.3, TPM can be emitted as a VOC or PM as outlined by the TCEQ Air Permit Division (TCEQ 2006b). Therefore, chronic ReVs and ESLs were derived for TPM as outlined in the following sections based on whether TPM was considered a VOC or PM.

4.1.3 PODs for the Key Study and Dosimetric Adjustments

The NOAEL of 1,000 mg/kg was converted to an inhalation equivalent using route-to-route extrapolation (Appendices D-F). Male and female inhalation equivalents were determined separately using average body weights for rats in the 1,000 mg/kg treatment group, along with a generic male and female Sprague-Dawley rat inhalation rate (USEPA 1988) for the conversion to an inhalation equivalent. Male and female inhalation equivalents were then added together and averaged to be representative for both sexes. The inhalation equivalent POD_{ADJ} used was 1,335.8 mg/m^3.

4.1.3.1 VOC

As discussed previously in Section 3.1.3.1, there is not sufficient information to classify TPM as a category 1, 2 or 3 vapor for animal to human dosimetric adjustments. Therefore, no animal to human dosimetric adjustments were used for the chronic VOC evaluation of TPM. In lieu of a POD_{HEC}, the POD_{ADJ} from Section 4.1.3 was applied, resulting in a subchronic POD_{ADJ} for TPM as a VOC of 1,335,800 $\mu g/m^3$.

4.1.3.2 PM

Conditions for treating TPM as a mist are discussed previously in Section 3.1.3.2. The procedures for performing dosimetric adjustments described in that section are the same as those used for the chronic PM evaluation. The subchronic POD_{HEC} for TPM as PM = 1,637,400 µg/m^3.

4.1.4 Adjustments to the POD_{ADJ} and POD_{HEC}

4.1.4.1 VOC

The adjustments to the POD_{ADJ} discussed in Section 3.1.4.1 are the same as those used for the chronic VOC evaluation. The only difference is that a subchronic to chronic UF of 3 was also used (total UF = 1000). A subchronic to chronic UF of 3 was used because consistencies between the subchronic and subacute studies suggest that effects will not change with increased exposure duration. Rounding was carried out in this section as discussed in Section 3.1.4.1. The chronic ReV is 1,300 µg/m^3 (150 ppb), and the long-term ESL is 390 µg/m^3 (44 ppb) (Table 5).

4.1.4.2 PM

The adjustments to the POD_{HEC} discussed in Section 3.1.4.2 are the same as those used for the chronic PM evaluation. The only difference is that a subchronic to chronic UF of 3 was used (total UF = 300). A subchronic to chronic UF of 3 was used because consistencies between the subchronic and subacute studies suggest that effects will not change with increased exposure duration. Rounding was carried out in this section as discussed in Section 3.1.4.2. The chronic ReV is 5,400 µg/m^3 (Table 5). The long-term ESL would be 1,620 µg/m^3; however, the TS defaults to NAAQS values. Because the annual PM_{10} NAAQS value was recently revoked, a long-term ESL value cannot be identified for permitting purposes. However, the 24 h PM_{10} NAAQS must be met.

Table 5. Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Parameter	**Summary**	
Study	40 – 51 Day repeat dose and reproductive/developmental study (Faber and Hosenfeld 1992)	
Study Population	12 female; 12 male Sprague-Dawley rats per exposure group	
Study Quality	High (GLP)	
Exposure Method	40 – 51 day exposure via gavage @ 0, 100, 300, and 1,000 mg/kg	
Critical Effects	Freestanding NOAEL, no adverse effects observed	
POD (original study)	1,000 mg/kg (NOAEL)	
Exposure Duration	Once daily, 40 - 51 days	
POD_{ADJ} (Extrapolation to inhalation exposure)	1,335.8 mg/m^3	
POD_{ADJ} or POD_{HEC} Dosimetry adjustment from animal concentration to HEC	VOC POD_{ADJ} 1,335,800 µg/m^3	PM POD_{HEC} 1,637,400 µg/m^3 (mist with systemic effects, RDDR = 1.22)
Total UFs	1000	300
Interspecies UF	10	3
Intraspecies UF	10	10
LOAEL UF	NA	NA
Subchronic to chronic UF	3	3
Incomplete Database UF	3	3
Database Quality	Minimum	Minimum
Chronic ReV (HQ = 1)	1,300 µg/m^3 (150 ppb)	**5,400 µg/m^3**
Long-term ESL (HQ = 0.3)	**390 µg/m^3 (44 ppb)**	**---**

4.2 Carcinogenic Potential

Data are not available.

4.3 Welfare-Based Chronic ESLs

Data on vegetative effects are not available.

4.4 Long-Term Values

This chronic evaluation resulted in the derivation of the following chronic values:

TPM treated as a VOC:

- chronic ReV = 1,300 µg/m^3 (150 ppb)
- $^{chronic}ESL_{nonlinear(nc)}$ = 390 µg/m^3 (44 ppb)

TPM treated as PM:

- chronic ReV = 5,400 µg/m^3

The long-term ESLs for air permit evaluations are as follows: when treated as a VOC = 390 µg/m^3 (44 ppb) (Table 1).

References

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Appendix A: Calculations for Health-Based ^{acute}ESL: VOC

NOAEL = 1000 mg/kg
USEPA (1988) General Rat BW = 0.35 kg
USEPA (1988) Rat allometric equation for inhalation rate:
$I = 0.80\ x\ W^{0.8206} = 0.80\ x\ 0.35^{0.8206} = 0.3380\ m^3/day$

Route-to-Route Extrapolation:

$$Rat\ (mg/m^3) = \frac{NOAEL_{RAT}\ x\ BW\ x\ A}{Vh\ (m^3)}$$

NOAEL = No Observed Adverse Effect Level
BW = Body weight
A = Adsorption
Vh = Inhalation rate

$$Rat\ (mg/m^3) = \frac{1000\ mg/kg/day\ x\ 0.35\ kg\ x\ 1}{0.3380\ m^3/day}$$

= 1035.4 mg/m^3

Animal to Human NOAEL Extrapolation:

$NOAEL_{HEC} = NOAEL_A$
HEC = Human equivalent
A = Animal
$NOAEL_{HEC}$ = 1035.4 mg/m^3
= 1035.4 mg/m^3
= 1035400 µg/m^3 = POD_{HEC}

ReV and ^{acute}ESL Calculations:

$$ReV = \frac{POD_{HEC}}{UF_H\ x\ UF_A\ x\ UF_{Sub}\ x\ UF_L\ x\ UF_D}$$

UF_H = Human to human sensitivity
UF_A = Animal to human
UF_{Sub} = Subchronic to chronic

UF_L = LOAEL to NOAEL
UF_D = Incomplete to complete data

$$ReV = \frac{1035400\ \mu g/m^3}{10\ x\ 10\ x\ 3}$$

= 3400 µg/m^3
= 380 ppb

$^{acute}ESL = ReV\ x\ HQ$
= 3400 µg/m^3 x 0.3
= 1000 µg/m^3
= 110 ppb

NOTE: All intermediate or transitional calculations shown have been rounded to 5 significant figures for purposes of reporting in this document. However, in actual calculations, the entire number (without rounding) was carried from one intermediate equation to the next, with the exception of the ESL calculation (where the rounded ReV was carried into that equation). ReV and ESL values were rounded to two significant figures.

Appendix B: Calculations for Health-Based ^{acute}ESL: PM

NOAEL = 1000 mg/kg
USEPA (1988) General Rat BW = 0.35 kg
USEPA (1988) Rat allometric equation for inhalation rate:

$$I = 0.80\ x\ W^{0.8206} = 0.80\ x\ 0.35^{0.8206} = 0.3380\ m^3/day$$

Route-to-Route Extrapolation:

$$Rat\ (mg/m^3) = \frac{NOAEL_{RAT}\ x\ BW\ x\ A}{Vh\ (m^3)}$$

NOAEL = No Observed Adverse Effect Level
BW = Body weight
A = Adsorption
Vh = Inhalation rate

$$Rat\ (mg/m^3) = \frac{1000\ mg/kg/day\ x\ 0.35\ kg\ x\ 1}{0.3380\ m^3/day}$$

= 1035.4 mg/m^3

RDDR Calculation:

$$RDDR = \frac{Ve_A\ x\ DF_A\ x\ NF_H}{Ve_H\ x\ DF_H\ x\ NF_A}$$

RDDR = Regional Deposition Dose Ratio
Ve = Minute ventilation
DF = Deposition fraction in the respiratory tract target region
NF = Normalizer factor
A = Animal
H = Human

$$RDDR = \frac{137.3\ mL/\min\ x\ 0.999\ x\ 8800\ cm^2}{13800\ mL/\min\ x\ 0.998\ x\ 71.5\ cm^2}$$

= 1.2257

Animal to Human NOAEL Extrapolation:

$NOAEL_{HEC} = NOAEL_A$ x RDDR

HEC = Human equivalent

A = Animal

$NOAEL_{HEC}$ = 1035.4 mg/m^3 x 1.2258

= 1269.2 mg/m^3

= 1269200 µg/m^3 = POD_{HEC}

ReV and ^{acute}ESL Calculations:

$$ReV = \frac{POD_{HEC}}{UF_H \; x \; UF_A \; x \; UF_{Sub} \; x \; UF_L \; x \; UF_D}$$

UF_H = Human to human sensitivity

UF_A = Animal to human

UF_{Sub} = Subchronic to chronic

UF_L = LOAEL to NOAEL

UF_D = Incomplete to complete data

$$ReV = \frac{1269200 \; \mu g/m^3}{10 \; x \; 3 \; x \; 3}$$

= 13000 µg/m^3

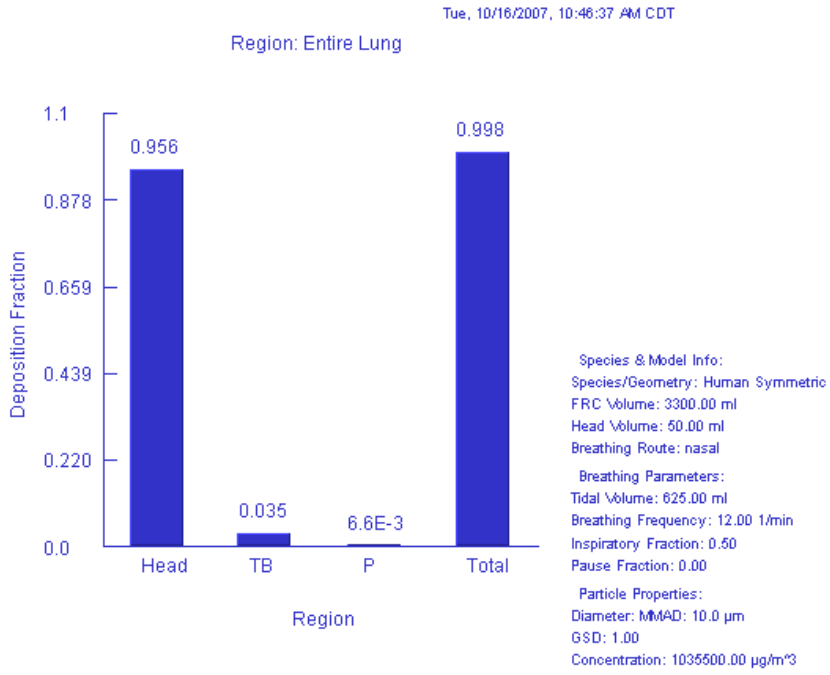
$^{acute}ESL = ReV \; x \; HQ$

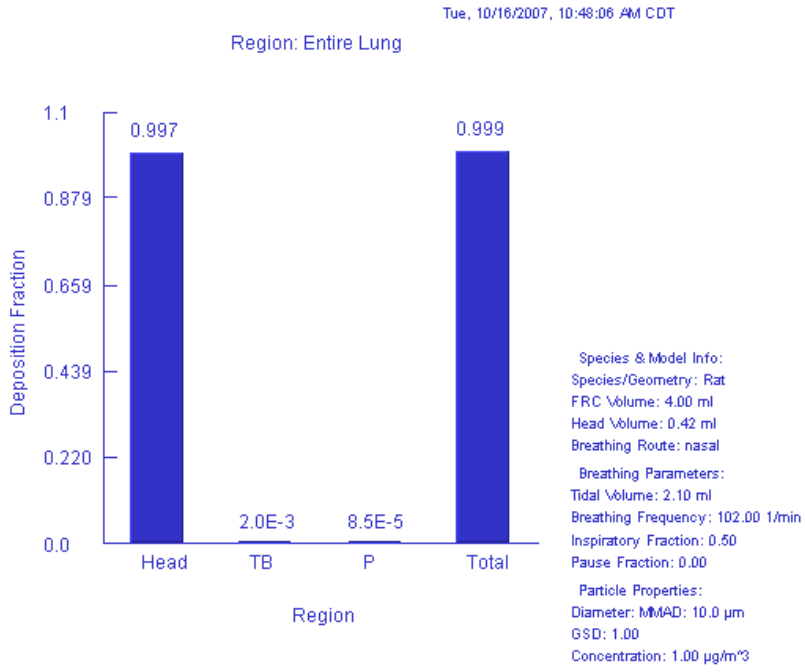
= 13000 µg/m^3 x 0.3

= 3900 µg/m^3

NOTE: All intermediate or transitional calculations shown have been rounded to 5 significant figures for purposes of reporting in this document. However, in actual calculations, the entire number (without rounding) was carried from one intermediate equation to the next, with the exception of the ESL calculation (where the rounded ReV was carried into that equation). ReV and ESL values were rounded to two significant figures.

Appendix C: MPPD Program Output for Subacute Study: PM





Appendix D: Calculations for Health-Based $^{chronic}ESL_{nonlinear(nc)}$: VOC

NOAEL = 1000 mg/kg

Average Subchronic Sprague-Dawley Body Weights for the 1000 mg/kg Treatment Groups (Faber and Hosenfeld 1992):

Mean BWrat, male = 390 g = 0.390 kg

Mean BWrat, female = 270 g = 0.270 kg

USEPA (1988) Sprague-Dawley Inhalation Rates:

$Male_{subchronic}$ = 0.27 m^3/day

$Female_{subchronic}$ = 0.22 m^3/day

Route-to-Route Extrapolation:

$$Rat\ (mg/m^3) = \frac{NOAEL_{RAT}\ x\ BW\ x\ A}{Vh\ (m^3)}$$

NOAEL = No Observed Adverse Effect Level

BW = Body weight

A = Adsorption

Vh = Inhalation rate

$$Rat_{male}\ (mg/m^3) = \frac{1000\ mg/kg/day\ x\ 0.390\ kg\ x\ 1}{0.27\ m^3/day}$$

= 1444.4 mg/m^3

$$Rat_{female}\ (mg/m^3) = \frac{1000\ mg/kg/day\ x\ 0.270\ kg\ x\ 1}{0.22\ m^3/day}$$

= 1227.3 mg/m^3

$$Rat_{average}\ (mg/m^3) = \frac{Rat_{male}\ (mg/m^3) + Rat_{female}\ (mg/m^3)}{2}$$

$$Rat_{average}\ (mg/m^3) = \frac{1444.4\ mg/m^3 + 1227.3\ mg/m^3}{2}$$

= 1335.8 mg/m^3

Animal to Human NOAEL Extrapolation:

$NOAEL_{HEC} = NOAEL_A$

HEC = Human equivalent

A = Animal

$NOAEL_{HEC}$ = 1335.8 mg/m^3

= 1335.8 mg/m^3

= 1335800 µg/m^3 = POD_{HEC}

ReV and ^{acute}ESL Calculations:

$$ReV = \frac{POD_{HEC}}{UF_H \; x \; UF_A \; x \; UF_{Sub} \; x \; UF_L \; x \; UF_D}$$

UF_H = Human to human sensitivity

UF_A = Animal to human

UF_{Sub} = Subchronic to chronic

UF_L = LOAEL to NOAEL

UF_D = Incomplete to complete data

$$ReV = \frac{1335800 \; \mu g/m^3}{10 \; x \; 10 \; x \; 3 \; x \; 3}$$

= 1300 µg/m^3

= 150 ppb

$^{acute}ESL = ReV \; x \; HQ$

= 1300 µg/m^3 x 0.3

= 390 µg/m^3

= 44 ppb

NOTE: All intermediate or transitional calculations shown have been rounded to 5 significant figures for purposes of reporting in this document. However, in actual calculations, the entire number (without rounding) was carried from one intermediate equation to the next, with the exception of the ESL calculation (where the rounded ReV was carried into that equation). ReV and ESL values were rounded to two significant figures.

Appendix E: Calculations for Health-Based $^{chronic}ESL_{nonlinear(nc)}$: PM

NOAEL = 1000 mg/kg

Average Subchronic Sprague-Dawley Body Weights for the 1000 mg/kg Treatment Groups (Faber and Hosenfeld 1992):

Mean BWrat, male = 390 g = 0.390 kg

Mean BWrat, female = 270 g = 0.270 kg

USEPA (1988) Sprague-Dawley Inhalation Rates:

$Male_{subchronic}$ = 0.27 m^3/day

$Female_{subchronic}$ = 0.22 m^3/day

Route-to-Route Extrapolation:

$$Rat\ (mg/m^3) = \frac{NOAEL_{RAT}\ x\ BW\ x\ A}{Vh\ (m^3)}$$

NOAEL = No Observed Adverse Effect Level

BW = Body weight

A = Adsorption

Vh = Inhalation rate

$$Rat_{male}\ (mg/m^3) = \frac{1000\ mg/kg/day\ x\ 0.390\ kg\ x\ 1}{0.27\ m^3/day}$$

= 1444.4 mg/m^3

$$Rat_{female}\ (mg/m^3) = \frac{1000\ mg/kg/day\ x\ 0.270\ kg\ x\ 1}{0.22\ m^3/day}$$

= 1227.3 mg/m^3

$$Rat_{average}\ (mg/m^3) = \frac{Rat_{male}\ (mg/m^3) + Rat_{female}\ (mg/m^3)}{2}$$

$$Rat_{average}\ (mg/m^3) = \frac{1444.4\ mg/m^3 + 1227.3\ mg/m^3}{2}$$

= 1335.8 mg/m^3

RDDR Calculation:

$$RDDR = \frac{Ve_A \; x \; DF_A \; x \; NF_H}{Ve_H \; x \; DF_H \; x \; NF_A}$$

RDDR = Regional Deposition Dose Ratio
Ve = Minute ventilation
DF = Deposition fraction in the respiratory tract target region
NF = Normalizer factor
A = Animal
H = Human

$$RDDR = \frac{137.3 \; mL/\min \; x \; 0.999 \; x \; 8800 \; cm^2}{13800 \; mL/\min \; x \; 0.998 \; x \; 71.5 \; cm^2}$$

= 1.2257

Animal to Human NOAEL Extrapolation:

$NOAEL_{HEC} = NOAEL_A \; x \; RDDR$

HEC = Human equivalent
A = Animal

$NOAEL_{HEC}$ = 1335.8 mg/m^3 x 1.2257
= 1637.4 mg/m^3
= 1637400 µg/m^3 = POD_{HEC}

ReV and ^{acute}ESL Calculations:

$$ReV = \frac{POD_{HEC}}{UF_H \; x \; UF_A \; x \; UF_{Sub} \; x \; UF_L \; x \; UF_D}$$

UF_H = Human to human sensitivity
UF_A = Animal to human
UF_{Sub} = Subchronic to chronic
UF_L = LOAEL to NOAEL
UF_D = Incomplete to complete data

$$ReV = \frac{1637400 \; \mu g/m^3}{10 \; x \; 3 \; x \; 3 \; x \; 3}$$

= 5400 µg/m^3

$^{acute}ESL = ReV \; x \; HQ$
= 5400 µg/m^3 x 0.3
= 1620 µg/m^3

NOTE: All intermediate or transitional calculations shown have been rounded to 5 significant figures for purposes of reporting in this document. However, in actual calculations, the entire number (without rounding) was carried from one intermediate equation to the next, with the exception of the ESL calculation (where the rounded ReV was carried into that equation). ReV and ESL values were rounded to two significant figures.

Appendix F: MPPD Program Output for Subchronic Study: PM