Ontario Air Standards

For

Trimethylbenzenes:

1,2,3-Trimethylbenzene
1,2,4-Trimethylbenzene
1,3,5-Trimethylbenzene

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Standards Development Branch

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Executive Summary

The Ontario Ministry of the Environment (MOE) has identified the need to develop and/or update air quality standards for priority contaminants. The Ministry's Standards Plan, which was released in October, 1996 and revised in November, 1999, identified candidate substances for which current air quality standards will be reviewed or new standards developed. 1,2,4-Trimethylbenzene was identified as a priority for review based on both its pattern of use in Ontario and toxicological information that has been published subsequent to the development of the existing standard in 1988. Exposures to individual TMB isomers would be expected to occur rarely, and would likely be restricted to unique occupational or experimental situations. Therefore, the Ministry is expanding the current AAQC and POI value to apply to all isomers of trimethylbenzene and to any mixtures of these isomers. Once a decision is made on the air standards, they will be incorporated into Ontario Regulation 419: Air Pollution – Local Air Quality (O. Reg. 419/05). The Ambient Air Quality Criterion (AAQC) will be incorporated into Schedule 3 of the regulation and the half hour standards will be incorporated into Schedule 2. An 'Information Document' containing a review of scientific and technical information relevant to setting an air quality standard for 1,2,4-trimethylbenzenes was previously posted on the Environmental Bill of Rights Registry for public comments. This was followed more recently by the posting of a document providing the rationale ('Rationale Document') for recommending an Ambient Air Quality Criterion (AAQC) and a half hour standard for trimethylbenzenes. This document, referred to as the 'Decision Document', summarizes the comments received from stakeholders on the proposed standards and the Ministry responses to these comments. This document also provides the rationale for the decision on the air quality standards for trimethylbenzenes.

Currently in Ontario, the MOE has established a 24-hour Ambient Air Quality Criterion (AAQC) and the half-hour Point of Impingement (POI) values for 1,2 4-Trimethylbenzene . Trimethylbenzene (TMB) isomers include 1,2,3-TMB (CAS# 526-73-8), 1,2,4-TMB (CAS# 95-63-6), and 1,3,5-TMB (CAS#108-67-8). The trimethylbenzenes are colourless, flammable liquids. The geometric mean of the odour detection threshold in air is reported at 12,000 µg/m^3 for 1,2,4-TMB and 10,700 µg/m^3 for 1,3,5-TMB.

All three trimethylbenzene isomers occur in refined petroleum and coal tars. 1,2,4-Trimethylbenzene has been reported as a major constituent (roughly 40 percent) of the petroleum refinery distillation fraction known as the C9 aromatic hydrocarbon fraction. The C9 fraction consists of nine-carbon aromatics, such as trimethylbenzenes and other alkyl benzenes. The vast majority (about 99% of the total volume produced) of the C9 fraction is used as a gasoline additive. The remaining portion of the C9 fraction is used in such applications as a solvent in coatings, pesticides, cleaners, and

printing and inks. Industries utilizing and processing trimethylbenzene isomers and other members of the C9 aromatic fraction may also be important sources (*e.g.*, petroleum refineries, nonferrous foundries, and various plastics products manufacturers). Vehicle emissions are a major anthropogenic source of 1,2,4-TMB, due to its widespread use as a gasoline additive. Trimethylbenzenes are also used by industries as chemical raw materials, paint thinners, and solvents. 1,2,4-TMB, is mainly used in the manufacture of trimellitic anhydride as a raw material. It can also be used in the manufacture of perfumes, dyes, pharmaceuticals, resins, and pseudocumidine.

The National Pollutant Release Inventory (NPRI) is a program by Environment Canada which identifies and monitors sources of pollution in Canada. Of the trimethylbenzene isomers, only 1,2,4-TMB is currently monitored through the NPRI program. According to the NPRI, a total of 739 tonnes of 1,2,4-TMB was released in Canada in 2003. In the years 1994 to 2003, Ontario contributed 63% of the total released in Canada, with its highest proportion occurring in 2001, when Ontario contributed 80% of the Canadian total. Vehicle emissions are a major anthropogenic source of 1,2,4-TMB (CalARB, 1995) due to its widespread use as a gasoline additive. NPRI data indicates that from 1998 to 2002, the primary contributor of 1,2,4-TMB in Canada were motor vehicle industries and those industries responsible for automotive accessories and parts.

Recently a number of studies have been conducted concerning the toxicokinetics of trimethylbenzenes. This compound appears to be readily absorbed from the lungs. Once in the blood stream it is primarily bound to red blood cells, and upon distribution within the body, accumulates in fatty tissues, as is expected based on its lipophilicity. Metabolism of the TMB isomers in humans and animals occurs by side-chain oxidation to form alcohols and carboxylic acids or hydroxylation to phenols, which are then conjugated with glucuronic acid, glycine, or sulphates prior to urinary excretion. Dimethylbenzoic acids are the main excreted metabolite of absorbed trimethylbenzenes as urinary excretion of these metabolites correlated well with the absorbed.

Central nervous system (CNS) and hematological effects have been reported in humans exposed to trimethylbenzene vapours concentrations up to 60 ppm (295 mg/m^3). Animal studies have provided further evidence of these critical effects with both acute and chronic exposure to trimethylbenzene isomers. One study investigated the potential developmental and reproductive effects due to exposure to 1,2,4-TMB and1,3,5-TMB. A NOEAL for prenatal developmental toxicity was identified at 300 ppm (1476 mg/m^3) for both compounds. It should be noted that maternal toxicity was identified at 300 ppm for 1,3,5-TMB. There is one chronic study on 1,2,4-TMB available which did not indicate that carcinogenic effects occur at a concentration lower than the NOAEL of 123 mg/m^3, which, as discussed later, is the concentration associated with the critical effect for this substance. In addition, similar compounds which have exhibited similar CNS effects observed with TMB (such as toluene and xylene) have not been assessed as a carcinogen by the Ministry or other major agencies.

Currently in Ontario, the 24-hour Ambient Air Quality Criterion (AAQC) and the half-hour Point of Impingement (POI) values are 1000 µg/m^3, and 500 µg/m^3, respectively for 1,2,4-TMB. The 24-hour AAQC is based on odour and health considerations, while the half-hour value is based on odour.

In revising the air quality standards for Ontario, the Ministry of the Environment is considering risk assessments and standards and guidelines used by environmental agencies world-wide. This report reviews the scientific basis for air quality guidelines and standards developed for trimethylbenzenes by the States of Michigan, New York, and Texas.

None of the regulatory agencies reviewed derived their air quality criteria directly from trimethylbenzene experimental data. The TLV-TWA derived by the ACGIH is the basis of all the available air quality criteria. The principal study (Battig *et al.*, 1956) used by the ACGIH is the only identified human epidemiological study available on trimethylbenzenes. However, there are several challenges to using the Battig *et al*. (1956) study which were not addressed in the ACGIH write-up for the TLV-TWA value.

Several subchronic rat studies examined the potential CNS effects associated with inhalation exposure to trimethylbenzenes. Behavioural effects were measured to assess potential CNS effects. 1,2,3-TMB varied in the specific behavioural effects observed and the reported concentration at which these effects were noted. Some behavioural effects were produced at 123 mg/m^3 and 492 mg/m^3 (Korsak and Rydzynski, 1996; Wiaderna *et al.*, 1998). 1,2,4-TMB produced similar behavioural effects are 492 mg/m^3 (Gralewicz, 1997; Gralewicz and Wiaderna, 2001), and 1,3,5-TMB produced behavioural effects (decreased pain sensitivity) at 492 mg/m^3 (Gralewicz and Wiaderna, 2001; Wiaderna *et al.*, 2002). Overall, this series of studies concluded that long-term CNS effects may follow a 4-week inhalation exposure to any of the TMB isomers at concentration as low as 492 mg/m^3. Upon reviewing these studies the weight of evidence supports a NOAEL of 123 mg/m^3 for trimethylbenzenes.

The NOAEL is then adjusted for continuous time, and a cumulative uncertainty factor of 100 is applied to derive the 24-hour AAQC value of ≈ 220 µg/m^3. The uncertainty factor of 100 incorporates a factor of 3 ($10^{½}$) for interspecies extrapolation, a factor of 10 for intraspecies variability and a factor of 3 ($10^{½}$) for subchronic to chronic extrapolation.

Based on an evaluation of the scientific rationale of air guidelines from leading agencies, an examination of current toxicological research, and comments from stakeholders, the following Air Quality Standards are set for trimethylbenzenes:

- **A 24-hour average AAQC of 220 µg/m^3 (micrograms per cubic metre of air) for trimethylbenzenes* based on the CNS effects of these compounds; and**

- **A half-hour standard of 660 µg/m^3 (micrograms per cubic metre of air) for trimethylbenzenes* based on the CNS effects of these compounds.**

* Note: The AAQC and half-hour POI standard will apply to any isomer of trimethylbenzene (i.e. 1,2,3-TMB (CAS# 526-73-8) or 1,2,4-TMB (CAS# 95-63-6) or 1,3,5-TMB (CAS#108-67-8)) or to any mixture of these isomers.

These effects-based standards (which include the AAQCs and the corresponding effects-based half hour standards) will be incorporated into Ontario Regulation 419/05: Air Pollution – Local Air Quality (O. Reg. 419/05). The AAQCs will be incorporated into Schedule 3 of O. Reg. 419/05; the half-hour standard will be incorporated into Schedule 2.

MOE generally proposes a phase-in for new standards or standards that will be more stringent than the current standard or guideline. The phase-in for trimethylbenzenes is set out in O. Reg. 419/05.

Among other things, O. Reg. 419/05 sets out the applicability of standards, appropriate averaging times, phase-in periods, types of air dispersion model and when various sectors are to use these models. There are 3 guidelines that support O. Reg. 419/05. These guidelines are:

- "Guideline for the Implementation of Air Standards in Ontario" (GIASO);
- "Air Dispersion Modelling Guideline for Ontario" (ADMGO); and
- "Procedure for Preparing an Emission Summary and Dispersion Modelling Report" (ESDM Procedure).

GIASO outlines a risk-based decision making process to set site specific alternative air standards to deal with implementation barriers (time, technology and economics) associated with the introduction of new/updated air standards and new models. The alternative standard setting process is set out in section 32 of O. Reg. 419/05.

For further information on these guidelines and O. Reg. 419/05, please see the Ministry's website http://www.ontario.ca/environment and follow the links to local air quality.

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1.0 Introduction

Ontario regulates air emissions in order to achieve and maintain air quality which is protective of human health and the environment. The *Environmental Protection Act* (Section 9) requires stationary sources that emit, or have the potential to emit, a contaminant to obtain a Certificate of Approval which outlines the conditions under which the facility can operate.

The Ministry of the Environment uses a combination of regulated point of impingement (POI) standards and guidelines (MOE, 2005) in reviewing Emission Summary and Dispersion Modelling Reports submitted to support a Certificate of Approval application or a Ministry request for a compliance assessment. Ambient Air Quality Criteria form the basis for an air standard or guideline and represent human health or environmental effects-based values, normally set at a level not expected to cause adverse effects based on continuous exposure. As such, factors such as technical feasibility and costs are not considered when establishing AAQCs or the equivalent half hour standards which are derived from the AAQCs using a mathematical scaling factor. The risk based process for alternative standards, as set out in section 32 of O. Reg. 419/05, is the mechanism created to deal with the time, technical and economic issues. The Guideline for the Implementation of Air Standards in Ontario (GIASO) is the supporting document for stakeholders who are interested in more information on alternative standards. For further information on O. Reg. 419/05 and GIASO, please see the Ministry's website http://www.ene.gov.on.ca/envision/air/regulations/localquality.htm.

Air standards referenced in O. Reg. 419/05 are used for compliance and enforcement. Dispersion modelling, as referenced in the regulation, is used to relate emission rates from a source to resulting concentrations of a particular contaminant. Air standards specified under O. Reg. 419/05 apply to stationary sources only.

In addition to air standards established under O. Reg. 419/05, the Ministry also has a large number of guidelines (including AAQCs). Similar to standards, guidelines are used by the Ministry to assess general air quality and the *potential* for causing adverse effect (MOE, 2005). Like the air standards specified in O. Reg. 419/05, guidelines (and now AAQCs) are used in reviewing Emission Summary and Dispersion Modelling reports submitted in support of applications for Certificates of Approval, to approve new and modified emission sources or other requirements. Once incorporated into a legal instrument such as a Certificate of Approval, guidelines can become legally binding.

The Ontario Ministry of the Environment continues to develop and/or update air standards for priority toxic contaminants. The Ministry's Standards Plan, which was released in October 1996 and revised in November 1999 (MOEE, 1996 & MOE, 1999), identified candidate substances for which current air standards will be reviewed. The

MOE 1999 Standards Plan outlines a multi-step process for developing air quality standards (MOE, 1999). Each standard has undergone a two step consultation process involving postings on the Environmental Registry, under the Environmental Bill of Rights (EBR):

- Information Drafts (Risk assessment/science review only)
- Rationale Documents (Proposed numerical limits)

1,2,4-Trimethylbenzene was identified as a priority for review based on its pattern of use in Ontario, and recent toxicological information. The initial step, an Information Draft (MOE, 2005), provided risk assessment information relevant to establishing a standard for a particular substance. This provided stakeholders with the opportunity to critically review the information and provide any additional information they felt should be considered by the Ministry in setting an air quality standard for a particular compound. The Ministry considered comments received on the Information Draft and recommended proposed standards for trimethylbenzenes: Ambient Air Quality Criterion (AAQC) and a half hour point of impingement (POI) standard, in a Rationale Document (MOE, 2006) and again solicited comments from stakeholders by posting on the Environmental Registry. After assessing comments on the Rationale Document the Ministry has finalized its work by making a decision on the air quality standards for trimethylbenzenes. This decision, which also highlights key comments from stakeholders on the proposed standards and the responses provided by the MOE, is documented by posting a Decision Notice (and supporting 'Decision Document', which provides the rationale for the decision on the air quality standards) onto the Environmental Registry.

In the 1999 Standards Plan, MOE made a commitment to consider time, technical, and economic issues for air standards and develop a risk management framework to address implementation issues. The risk-based framework has been developed and is part of O. Reg. 419/05. The alternative standards setting process is a risk-based process that considers time, technical and economic issues on a site specific basis. For further information on Regulation 419/05 and the process for requesting an alternative site specific air standard, please see the Ministry's website and follow the links to local air quality.

2.0 General Information

2.1 Physical and Chemical Properties

The trimethylbenzenes (TMB) are colourless, flammable liquids (ACGIH, 2002a; Verschueren, 1983). 1,2,4-TMB is practically insoluble in water, but is soluble in organic solvents such as alcohol, ether, and benzene (Budavari *et al.*, 1996; HSDB, 2002). The geometric mean of the odour detection threshold in air is reported at 12,000 µg/m^3 for 1,2,4-TMB and 10,700 µg/m^3 for 1,3,5-TMB (AIHA, 1989).

Chemical and physical properties of the three isomers are similar to each other, as summarized by the ACGIH (ACGIH, 2001). The following list provides some specific information on the individual trimethylbenzene isomers and their properties (Budavari, 1989; Budavari *et al.*, 1996; Chemfinder, 2003; HSDB, 2002; Cavender, 1994; Sax and Lewis, 1987; U.S. EPA, 1987):

Chemical Name	**1,2,3-TMB**	**1,2,4-TMB**	**1,3,5-TMB**
CAS Number	526-73-8	95-63-6	108-67-8
RTECS #	DC3300000	DC3325000	OX6825000
Common Synonyms	hemellitol, hemimellitine	asymmetrical trimethylbenzene, pseudocumene, pseudocumol, psi-cumene	3,5-dimethyltoluene, Fleet-X, sym-trimethylbenzene, trimethylbenzol, mesitelene, mesitylene
Molecular Formula	C_9H_{12}		
Molecular Weight	120.19		
Melting Point	-26 °C	-43.78 °C	-44.8 °C
Boiling Point	176 °C	169-171 °C	164.7 °C
Henry's Law Constant	N/A	5.18×10^{-3} atm-cu m/mole	7.7×10^{-3} atm-cu m/mole
Flash Point	44 °C	54.4 °C	50 °C

Chemical Name	1,2,3-TMB	1,2,4-TMB	1,3,5-TMB
Water Solubility	Low solubility	Practically insoluble	Insoluble
Log K_{OW}	N/A	3.78	3.42
Log K_{OC}	N/A	3.5	2.9
Specific Gravity (water=1)	0.8944	0.8761	0.8637
Vapour Density (air=1)	4.14	4.15	4.14
Vapour Pressure	1 mm Hg @ 16.8 °C	2.03 mm Hg @ 25°C	2.48 mm Hg @ 25 °C
Conversion Factors @ 25°C	1 ppm = 4.92 mg/m^3 1 mg/m^3 = 0.2 ppm		

2.2 Production and Uses of Trimethylbenzenes

All three trimethylbenzene isomers occur in refined petroleum and coal tars (Bingham *et al.*, 2001). 1,2,4-TMB has been reported as a major constituent (roughly 40 percent) of the petroleum refinery distillation fraction known as the C9 aromatic hydrocarbon fraction (U.S. EPA, 1994a). The C9 fraction consists of nine-carbon aromatics, such as trimethylbenzenes and other alkyl benzenes. The vast majority (about 99% of the total volume produced) of the C9 fraction is used as a gasoline additive. Vehicle emissions are a major anthropogenic source of 1,2,4-TMB, due to the widespread use of the C9 fraction as a gasoline additive. The remaining portion of the C9 fraction is used in such applications as a solvent in coatings, pesticides, cleaners, and printing and inks. Industries utilizing and processing trimethylbenzene isomers and other members of the C9 aromatic fraction may also be important sources (*e.g.*, petroleum refineries, nonferrous foundries, and various plastics products manufacturers). The C9 fraction is produced in the United States at an annual estimated volume of 80 billion pounds (U.S. EPA, 1991). 1,2,4-TMB is isolated from the C9 fraction at an estimated rate of about 10 million pounds annually (U.S. EPA, 1994a).

Trimethylbenzenes are also used by industries as chemical raw materials, paint thinners, and solvents (Bingham *et al.*, 2001). 1,2,4-TMB, on its own, is mainly used in the manufacture of trimellitic anhydride as a raw material (HSDB, 2002; U.S. EPA,

1994a). Other uses include the manufacture of perfumes, dyes, pharmaceuticals, resins, and pseudocumidine (HSDB, 2002; Sax and Lewis, 1987). Specifically, 1,3,5-TMB is used as dyestuff intermediates, solvents, paint thinners and as a UV oxidation stabilizer for plastics (HSDB, 2005).

2.3 Sources and Levels

The National Pollutant Release Inventory (NPRI) is a program by Environment Canada which identifies and monitors sources of pollution in Canada. Of the trimethylbenzene isomers, only 1,2,4-TMB is currently monitored through the NPRI program. According to the National Pollutant Release Inventory (NPRI), a total of 739 tonnes of 1,2,4-TMB was released in Canada in 2003. Two-hundred and thirty-nine facilities have reported emitting 1,2,4-TMB into the atmosphere in 2003. The reported air releases of 1,2,4-TMB in Canada in 1995, 1996, 1997, 1998, 1999, 2000, 2001, and 2002 were 388, 363, 739, 669, 631, 581, 679 and 999 tonnes, respectively. The large increase of 1,2,4-TMB emissions between 2001 and 2002 are due to an increase in facilities reporting to NPRI. Ontario was identified as the primary contributor of 1,2,4-TMB. In the years of 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002 and 2003 Ontario released 210, 209, 338, 493, 481, 399, 544, 520 and 461 tonnes of 1,2,4-TMB. Over this time period, Ontario contributed an average of 63% of the total released in Canada, with its highest proportion occurring in 2001, when Ontario contributed 80% of the Canadian total.

Vehicle emissions are a major anthropogenic source of 1,2,4-TMB (CalARB, 1995), due to its widespread use as a gasoline additive. Industries utilizing and processing this compound and the C9 fraction may also be important sources. For example, in California, the major sources of 1,2,4-TMB are petroleum refining plants, nonferrous foundries, and various plastics products manufacturers (CalARB, 1997b). Natural sources of this compound include coal tar and a variety of petroleum deposits (HSDB, 1993). According to the NPRI data from 1998 to 2002, the primary contributor of 1,2,4-TMB in Canada were motor vehicle industries and those industries responsible for automotive accessories and parts.

Trace quantities of trimethylbenzenes have been detected in urban air (Bertch *et al.*, 1974). In the United States, urban areas had an average atmospheric level of 1,2,4-TMB of 5.9 $\mu g/m^3$, while that of rural areas was 2.9 $\mu g/m^3$ (U.S. EPA, 1988). A study by Chan *et al.* (1991) done in Raleigh, North Carolina in 1988, examined volatile organic compounds (VOCs) related to gasoline. During the study, the average ambient concentration of 1,2,4-TMB was found to be 2.7 $\mu g/m^3$, with a maximum concentration of 13.7 $\mu g/m^3$ (Chan *et al.*, 1991). Within vehicles, the mean concentration was 15.6 $\mu g/m^3$ and the maximum concentration was 39.0 $\mu g/m^3$ (Chan *et al.*, 1991). A study by Dann and Wang (1989) measured VOCs at 11 sites within the Greater Vancouver Regional District (GVRD). Mean concentrations of 1,2,4-TMB ranged from

4.4 to 22.1 µg/m^3, while the maximum levels were as high as 36.5 µg/m^3 (Dann and Wang, 1989).

Under the National Air Pollution Surveillance program (NAPS) 1,2,4-TMB was measured in ambient air by Environment Canada in a number of 24-hour samples collected across Canada between the years of 1993 and 2000 (Dann, 2002). More than forty different suburban, rural and urban locations in eight provinces were used. In examining the data set collected, the values ranged from non-detectable up to 36.1 µg/m^3 (Dann, 2002). The mean concentration of 1,2,4-TMB for the years of 1993-2000 was calculated to be approximately 0.57 µg/m^3.

2.4 Environmental Fate

The production and use of 1,2,4-TMB and 1,3,5-TMB may result in its release to the environment through various waste streams (Bingham *et al.* 2001).

1,2,4-TMB will exist solely in the vapour phase in the ambient atmosphere (HSDB, 2002). Vapour-phase 1,2,4-TMB is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals with estimated half-lives of 6 hours (U.S. EPA 1987) and 12 hours (Atkinson, 1989), and nitrate radicals with half-lives of 6 to 30 days (Carlier *et al*., 1988). 1,2,4-TMB also reacts with ozone, however the rate of its reaction is extremely slow with a reported half-life of 8820 days (Atkinson and Carter, 1984). With limited solubility in water, 1,2,4-TMB will not be readily transferred to soil via wet deposition.

In soil, 1,2,4-TMB will have low mobility (HSDB, 2002), a conclusion based on an estimated K_{oc} value of 720 (SRC, 2003) and a mobility classification scheme by Swann et al. (1983). Volatilization from moist and dry soil surfaces is expected to be the major fate process (HSDB, 2002; U.S. EPA, 1987). In one study, complete removal of 1,2,4-TMB occurred in 5 days, probably through evaporation (Dean-Ross, 1993). 1,2,4-TMB may also undergo significant aerobic biodegradation in both soil and water. In two studies, significant removal (via biodegradation) occurred after 7 days (Acton and Barker, 1992), whereas in the other, complete removal occurred within 8 days (Hutchins, 1991). However, high concentrations (500 mg/L) of 1,2,4-TMB may be toxic to the indigenous microbial population (Marion and Malaney, 1964). Anaerobic degradation (i.e., in groundwater) will likely be a minor process (Hutchins, 1991).

1,2,4-TMB is expected to volatilize rapidly from water surfaces, with estimated half-lives for a model river and model lake of 3 hours and 4 days, respectively (Lyman *et al*., 1990). However, since 1,2,4-TMB may adsorb moderately to sediment or particulate matter (HSDB, 2002; U.S. EPA, 1987), this process may be attenuated. 1,2,4-TMB is also expected to photodegrade rapidly in natural waters, with 81% degradation reported for pond water following exposure to sunlight for 21 days (Smith and Harper, 1982).

3.0 Toxicology of Trimethylbenzenes

The following toxicological review of trimethylbenzenes is focused on the inhalation route of exposure, as this is the predominant route of human exposure to TMB in air. Data on other exposure routes are included in this review only where relevant or where inhalation exposure data are lacking.

It should be noted that under most environmental exposure conditions, inhalation exposure to trimethylbenzenes would likely occur as a mixture of all three isomers: 1) 1,2,3-TMB (hemimellitene); 2) 1,2,4-TMB; and 3) 1,3,5-TMB (mesitylene). Trimethylbenzene is generally considered to be a mixture of these three isomers in various proportions. Thus, exposures to individual TMB isomers would be expected to occur only rarely, and would likely be restricted to unique occupational or experimental situations.

There has been a significant amount of research conducted recently on the toxicokinetics of 1,2,4-TMB, with the publication of a physiologically-based toxicokinetic (PBTK) model (Jarnberg and Johanson,1999) and several studies examining the toxicokinetics of 1,2,4-TMB in humans (Ichiba *et al*., 1992; Jarnberg *et al*., 1997; Jarnberg *et al*., 1996; Kostrzewski *et al.,* 1997).

Absorption for 1,2,3-TMB, 1,2,4-TMB and 1,3,5-TMB in humans following a 2-hour exposure during light exercise was 56%, 64% and 62%, respectively (Jarnberg *et al.* 1996). In this study, 10 males were exposed to 25 ppm (123 mg/m^3) of TMB vapour. Kostrzewski *et al.* (1997) reported that the lung absorption in humans of 1,2,3-TMB, 1,2,4-TMB and 1,3,5-TMB was 71%, 68%, and 67%, respectively. This study exposed 5 volunteers for 4-hours to 100 or 150 mg/m^3 of TMB. Trimethylbenzenes have also been reported to be readily absorbed following oral exposure (Huo *et al*., 1989; Sandmeyer, 1981; U.S. EPA, 1987). In the bloodstream, approximately 85% of 1,2,4-TMB is bound to red blood cells (U.S. EPA, 1988). As it distributes to tissues in humans, trimethylbenzenes tends to accumulate in adipose and fatty tissues, brain tissue, and perirenal fat, due to its lipophilicity (Jarnberg *et al*., 1996; Kostrzewski *et al.*, 1997; Jarnberg and Johanson, 1999; Zahlsen *et al.*, 1990). Trimethylbenzenes have also been reported to possess the ability to cross the placental barrier (Dowty *et al.*, 1976).

Metabolism of the TMB isomers in humans and animals occurs by side-chain oxidation to form alcohols and carboxylic acids or hydroxylation to phenols, which are then conjugated with glucuronic acid, glycine, or sulphates prior to urinary excretion (Kostrzewski *et al.*, 1997; Huo *et al*., 1989; U.S. EPA 1988; Mikulksi and Wiglusz, 1975). A high concentration of 1,2,4-TMB was measured in the liver of male Wistar rats following exposure to 1,2,4-TMB vapours at 492 or 1230 mg/m^3 via inhalation for 6 hours, single exposure (Swiercz *et al.* 2003), suggesting that metabolism of 1,2,4-TMB in the rat occurs mainly in the liver. Swiercz *et al.* (2003) reported that the elimination of

1,2,4-TMB from venous blood after chronic exposure followed an open two-compartment model. Urinary excretion of dimethylbenzoic acid metabolites in humans occurs in accordance with the open two compartment model. The open two compartment model is used to model lipophilicity. (Jarnberg *et al*., 1996; Jarnberg and Johanson, 1999; Kostrzewski *et al.,* 1997). At the end of a 14-day study in rats exposed to 4920 mg/m^3, a brain/blood ratio of 2.0 and a fat/blood ratio of 63 were determined for 1,2,4-TMB (Zahlsen *et al.,* 1990).

Dimethylbenzoic acids are the main excreted metabolites of absorbed trimethylbenzenes as urinary excretion of these metabolites correlated well with the absorbed dose (Bingham *et al.*, 2001). 3,4-Dimethylhippuric acid has been reported to be a minor metabolite in humans (Fukaya *et al*., 1994; Ichiba *et al*., 1992; Jarnberg *et al.,* 1997). This metabolite has also been observed in rabbits, in addition to 2,4-dimethylbenzoic acid (HSDB, 2002; U.S. EPA, 1988; Cerf *et al.,* 1980). In humans, approximately 22% of the total inhaled 1,2,4-TMB was excreted as the dimethylhippuric acid metabolite within 24h. Similarly, only 11% was observed for 1,2,3-TMB and 3% 1,3,5-TMB (Jarnberg *et al.,* 1997b). Half-times for urinary metabolites were reported as 9.5 hours for glycine conjugates, 22.9 hours for glucuronide conjugates, 37.6 hours for sulphate conjugates (U.S. EPA, 1988), and 3.7 hours for 3,4-dimethylhippuric acid (Jarnberg *et al.,*1997). In general, concentrations of TMB isomers or their metabolites (dimethylbenzoic acid) in exhaled air, blood, or urine may be suitable biomarkers of exposure (Fukaya *et al*., 1994; Ichiba *et al*., 1992; Jarnberg *et al.,* 1997; Kostrzewski *et al.,* 1997).

Jarnberg *et al.* (1998) compared the toxicokinetics of inhaled white spirits which contained approximately 4% 1,2,4-TMB to inhaled 1,2,4-TMB alone. Nine men were exposed to 300 mg/m^3 for 2 hours. The same volunteers were exposed to 1,2,4-TMB at 2 ppm (10 mg/m^3) and 24 ppm (118 mg/m^3) in a previous study 1 year earlier, see Jarnberg *et al.* (1996). This study found that blood levels of 1,2,4-TMB was significantly higher during and after exposure to white spirits compared to exposure to 1,2,4-TMB alone and concluded that a component of white spirits interfered with the elimination of 1,2,4-TMB.

In summary, trimethylbenzenes appear to be readily absorbed from the lungs. Once in the blood stream it is primarily bound to red blood cells, and upon distribution within the body, accumulates in fatty tissues, as is expected based on its lipophilicity. Metabolism of the TMB isomers in humans and animals occurs by side-chain oxidation to form alcohols and carboxylic acids or hydroxylation to phenols, which are then conjugated with glucuronic acid, glycine, or sulphates prior to urinary excretion. Dimethylbenzoic acids are the main excreted metabolite of absorbed trimethylbenzenes as urinary excretion of these metabolites correlated well with the absorbed.

3.1 Acute Toxicity

There is limited acute toxicological information available for 1,2,3-TMB or 1,3,5-TMB alone. Generally, the primary acute effect of inhalation or exposure to trimethylbenzene (mixed isomers) is eye, nose, and respiratory irritation. It is also a primary skin irritant. High concentration of 1,3,5-TMB (24,550 to 44,190 mg/m^3) caused central nervous system (CNS) depression in mice (ACGIH 2001).

Symptoms of acute effects in humans following exposure to 1,2,4-TMB via inhalation include eye, nose and respiratory irritation and pneumonitis (ACGIH, 2002a; HSDB, 2002). Inhalation of high concentrations of the vapour (*i.e.*, 24,600 mg/m^3 to 44,300 mg/m^3) may cause headache, fatigue, and drowsiness, and other symptoms of CNS depression (HSDB, 2002; ACGIH, 1991; U.S. EPA, 1994). Jarnberg *et al.* (1997) reported no irritation or CNS depression in 9 healthy male volunteers exposed for 2 hours via inhalation to 11 mg/m^3 1,2,4-TMB.

The irritative effects of TMBs on the respiratory system were studied by Korsak *et al.* (1997). Sensory irritation was quantified by measurements of the respiratory rate in mice. Korsak *et al.* (1997) suggest that that the depression of the respiratory rate in mice correlates with the extent of eye and respiratory irritation in man. Group of 810 male Balb/C mice were exposed for 6 minutes to a TMB isomer. The concentration depressing the respiratory rate in mice to 50% (RD_{50}) was measured. The RD_{50} for 1,2,3-TMB, 1,2,4-TMB and 1,3,5-TMB was reported at 541, 578 and 519 ppm, respectively. From this study, an occupational limit for trimethylbenzenes based on RD_{50} values was suggested to be between 10 to 30 ppm.

In a study by Korsak *et al*. (1995) the neurotoxic and sensory respiratory irritation effects of 1,2,4-TMB in male rats and male Balb/C mice were investigated with acute exposure. Rotarod performance and pain sensitivity behaviour were tested in rats exposed to 1,2,4-TMB at concentrations of 1230 to 9840 mg/m^3 immediately following a 4-hour exposure. Exposure resulted in concentration-dependent effects on rotarod performance and a decrease in pain sensitivity in rats. The authors reported an Effective Concentration$_{50}$ (EC_{50}) value for rotarod performance behaviour effects as 4693 mg/m^3 and reported an EC_{50} value of 5682 mg/m^3 for the observed decrease in pain sensitivity. The respiratory rate was measured for Balb/C male mice while exposed to 1,2,4-TMB for 6 minutes. The concentration found to cause a 50% depression in the respiratory rate (RD_{50}) was reported as 2843 mg/m^3.

Korsak and Rydzynski (1996) also reported rotarod performance and pain sensitivity behaviour for 1,2,3- TMB and 1,3,5-TMB. Rats were exposed to concentrations of 1230 to 9840 mg/m^3 of a TMB isomer for 4-hours. Immediately following exposure a rotarod performance was conducted. The rotarod performance behaviour disturbance (EC_{50}) value for 1,2,3-TMB and 1,3,5-TMB was reported at 3779 and 4738 mg/m^3 respectively.

In addition to this acute study performed, Korsak and Rydzynski (1996) also carried out a subchronic study and reported on this in the same research paper.

CNS effects have been reported in mice and rats following acute inhalation exposure to 1,2,4-TMB concentrations ranging between 4700 to 44,300 mg/m^3 (Lazarew, 1929; Cameron *et al.*, 1938; Korsak and Rydzynski, 1996), while transient alteration in white blood cell counts were observed in rats exposed to 1,2,4-TMB concentrations ranging between 1500 to 6000 mg/m^3 for 6 hours (Wiglusz *et al.*, 1975). The LC_{50} for rats has been reported to be 18,000 mg/m^3 following a 4-hour inhalation exposure to 1,2,4-TMB (RTECS, 2000).

3.2 Subchronic and Chronic Toxicity

Symptoms related to long-term inhalation exposure of humans to solvents containing 1,2,4-TMB have been reported to include nervousness, tension, bronchitis, headaches, drowsiness, and vertigo (Battig *et al.,* 1956; U.S. EPA, 1988; 1994; HSDB, 2002).

Battig *et al.* (1956) investigated 27 employees that worked with a paint solvent which contained 30% 1,3,5-TMB and 50% 1,2,4-TMB for an unspecified number of years. Vapour concentrations ranged from 10 to 60 ppm (49 to 295 mg/m^3). A significant number of exposed individuals reported CNS changes, related to the effects described above, asthmatic bronchitis, and hematological effects. Anaemia and alterations in blood clotting were reported. A LOAEL of 295 mg/m^3 was identified for the observed CNS and hematological effects, as well as the development of bronchitis. The reported hematological effects, in addition to the observed CNS effects and the development of bronchitis, formed the basis for the ACGIH's TLV-TWA of 123 mg/m^3 for both the individual isomers of trimethylbenzene or any mixture containing them (ACGIH, 2002a,b). It has been suggested, however, that the hematological effects may have been due to trace amounts of benzene present in the solvent mixture (Gerarde, 1960; U.S. EPA, 1987).

Laboratory studies have yielded mixed results regarding the hematological effects of TMB. In a subchronic study, Wiglusz *et al.* (1975) found no significant hematological effects in rats exposed to 3000 mg/m^3 of 1,3,5-TMB (6 hours/day, 5 weeks), whereas Bernshtein (1972) reported inhibition of leukocyte phagocytic activity in rats exposed to a mixture of trimethylbenzene isomers at 1000 mg/m^3 (4 hours/day, 6 months).

Studying the neurotoxicity of the C9 aromatic fraction, Rees (1989) reported no neurological effects at concentrations of up to 7380 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks in male Sprague-Dawley rats. In addition to the acute study performed, Korsak and Rydzynski (1996) also reported in the same research paper a concentration-dependent disturbances in rotarod performance and decreased pain sensitivity in male Wistar rats following inhalation to 1,2,4-TMB or 1,2,3-TMB at concentrations of 123, 492

or 1230 mg/m^3, for a period of 6 hours/day, 5 days/week, for 3 months. Statistically significant disturbances in rotarod performance were observed at 492 and 1230 mg/m^3 for 1,2,3-TMB and only 1230 mg/m^3 for 1,2,4-TMB. These effects were more pronounced in rats exposed to 1,2,3-TMB. It should be noted that no recovery in rotarod performance was observed two weeks post-exposure.

In more recent studies by Korsak *et al*. (2000a, 2000b), Wistar rats were exposed to either 1,2,4-TMB or 1,2,3-TMB vapour at concentrations of 123, 492 or 1230 mg/m^3, for a period of 6 hours/day, 5 days/week, for 3 months. Effects other than neurotoxicity were examined, which include relative organ weights, hematological parameters, enzyme parameters and histopathological parameters.

Korsak *et al.* (2000a) reported an overall low degree of systemic toxicity associated with exposure to 1,2,4-TMB. There were no changes found in body weight gain, food consumption, and absolute and relative organ weights. Slightly higher activity of sorbitol dehydrogenase was observed in the male rats exposed at all concentration levels. The study also noted effects on hematological parameters characterized by a decrease in red blood cells and increase in white blood cells with exposure to 1230 mg/m^3 in male rats. Proliferation of peribronchial lymphatic tissue and interstitial lymphocytic infiltration were also observed in the male and female rats exposed to 492 and 1230 mg/m^3 of 1,2,4-TMB. NOEL values of 123 mg/m^3 were reported for female rats for clinical chemistry parameters, like sorbitol dehydrongenase activity. A NOEL of 1230 mg/m^3 was reported for female rats and hematological parameters, and a NOEL of 123 mg/m^3 was reported for pathological changes in the lower respiratory system, both for male and female rats.

Korsak *et al.* (2000b) exposed Wistar rats to 1,2,3-TMB. They found no changes in body weight gain and food consumption. At 1230 mg/m^3, an increase in liver weight was observed in male rats. A slight increase in sorbitol dehydrogenase was also noted in male rats, where as in females an increase of alkaline phosphatase activity. Also seen at 1230 mg/m^3 were a decreased red blood cell count and a slight increase in white blood cell, segmented neutrophil and lymphocyte count. Proliferation of the peribronchial lymphatic tissue, formation of lymphoepithelium in the bronchi, an increased number of goblet cells and interstitial lung parenchyma infiltration was also observed at 1230 mg/m^3. NOEL values of 1230 mg/m^3 were reported for female rats and sorbitol dehydrongenase activity, and male rats and alkaline phosphatase activity, following exposure to 1,2,3-TMB. Also, a NOEL of 492 mg/m^3 was reported for hematological parameters, and a NOEL of 123 mg/m^3 was reported for pathological changes in the lower respiratory system, both for male and female rats.

Both Korsak *et al.* (2000a, 2000b) concluded that the microscopically observed pathological changes in the lower respiratory system indicate relatively low toxic effect of 1,2,4-TMB and 1,2,3-TMB at concentration of 492 and 1230 mg/m^3.

Four experiments (Gralewicz *et al*., 1997; Wiaderna *et al.*, 1998; Gralewicz and Wiaderna, 2001; and Wiaderna *et al.* 2002) examined the behavioural effects associated with inhalation exposure to trimethylbenzenes. In the earlier study (Gralewicz *et al*., 1997), rats were exposed to 1,2,4-TMB at concentrations of 0, 123, 492, 1230 mg/m^3 for a period of 6 hours/day, 5 days/week, for 4 weeks. Behavioural effects were measured 14 and 54 days following the last exposure through radial maze performance (assay of short-term spatial memory), open field activity test (assay of spontaneous motor activity), step-down passive avoidance test (assay of long-term memory), active avoidance test (assay of the ability to learn and memorize), and the hot plate test (assay for analgesia (decreased pain sensitivity)). Behavioural effects were noted by the authors in both the open field and analgesia testing in those rats exposed to 492 or 1230 mg/m^3. Cognitive function was also found to be affected as learning of active avoidance was slightly reduced in rats exposed to 1230 mg/m^3. Wiaderna *et al.* (1998) performed the same study described above, however rats were exposed to 1,2,3-TMB. Behavioural effects were measured 14 and 61 days following the last exposure. It was found that rats exposed to 123 or 492 mg/m^3, but not 1230 mg/m^3, were significantly impaired in the passive avoidance testing, suggesting long-term memory effects. Rats exposed to 492 mg/m^3, but not 1230 mg/m^3, exhibited impaired active avoidance testing and hot plate testing, again, suggesting memory/learning effects and decreased pain sensitivity. Results are similar to the Gralewicz *et al.* (1997) study, however the effects of 1,2,3-TMB were seen at a lower concentration. In 2002, Wiaderna *et al.* performed the same study again, however rats were exposed to 1,3,5-TMB. The same effects were observed from 1,3,5-TMB as those observed in Gralewicz et al. (1997) study, and the Wiaderna *et al.* (1998) study. At 123 mg/m^3 significant difference were noted in passive and active avoidance tests, however 1,3,5-TMB was less effective. All studies concluded that inhalation exposure to TMB may lead to long-lasting disturbances in CNS functions. Wiaderna *et al.* (1998) and Gralewicz *et al.* (1997) reported a non-linear concentration/effect relationship and suggested that the concentration/effect curve for both 1,2,3-TMB and 1,2,4-TMB is an inverted “U”. Wiaderna *et al.* (2002) could not establish a concentration/effect relationship for1,3,5-TMB.

Gralewicz and Wiaderna (2001) also completed a comparative study on rats for CNS effects following inhalation exposure to m-xylene and trimethylbenzene isomers. Rats were exposed to 492 mg/m^3 of either m-xylene or one of the trimethylbenzene isomers for a period of 6 hours/day, 5 days/week for a total of 4 weeks. Similar effects were observed in this study as those previously reported in Gralewicz *et al.* (1997) and Wiaderna *et al.* (1998). It was concluded by the authors that the results of the series of studies performed do not indicate cognitive impairments as a result of TMB exposure. Rather the character of these alterations suggested a decreased ability to inhibit the locomotor response especially in fear-inducing situations. Interestingly, rats exposed to m-xylene at 492 mg/m^3 exhibited behavioural effects similar to those resulting from the TMB isomers exposure. This was not expected considering that CNS effects observed

following m-xylene exposure were usually noted at exposure concentrations much higher than 492 mg/m^3. In this study 1,3,5-TMB appeared to be as effective as 1,2,4-TMB and m-xylene. However, 1,2,3-TMB was apparently weaker than the other TMB isomers. Considering the previous studies conducted, which identified a "U" shaped concentration/effect curve of 1,2,3-TMB, it would appear that the 1,2,3-TMB concentration most effective in producing behavioural alterations is lower than 492 mg/m^3. Again, it was concluded that long-term behavioural alterations may follow a 4-week inhalation exposure to m-xylene, or any of the TMB isomers at concentration as low as 492 mg/m^3.

3.3 Developmental and Reproductive Toxicity

Only one study was identified which investigates the reproductive and developmental toxicity of trimethylbenzenes. Saillenfait *et al.* (2005) exposed pregnant rats to vapours of 1,2,4-TMB at concentration of 0, 100, 300, 600 or 900 ppm, and to 1,3,5-TMB at concentrations of 0, 100, 300, 600 and 1200 ppm. Exposure occurred on gestational days G6 through to G20, for 6 hours/day. Following the exposure period the pregnant rats were killed and their uteri were removed and weighed. The number of corpora lutea, implantation sites, resorptions, and dead and live fetuses were recorded. Live fetuses were weighted, sexed and examined for external anomalies. Half of the live fetuses were prepared and examined for internal soft tissue changes, and the other half were prepared and examined for skeletal changes. Maternal toxicity, as defined by a significant decrease in body weight gain and food consumption, was identified at 300 ppm for 1,3,5-TMB and 600 ppm for 1,2,4-TMB. No adverse effects were noted on embryo/fetal viability or morphology up to highest dosages for both 1,2,4-TMB and 1,3,5-TMB. Fetal growth retardations were noted at 600 ppm for both 1,2,4-TMB and 1,3,5-TMB. A NOEAL for prenatal developmental toxicity was identified at 300 ppm (1476 mg/m^3) for both compounds.

Limited data is available on the reproductive and developmental toxicity of the C9 aromatic fraction. Researchers at the International Research and Development Corporation for the American Petroleum Institute have conducted several studies of the C9 fraction, which were submitted to the U.S. EPA for review (as cited in: U.S. EPA, 1994a).

A three-generation reproductive study was conducted, which involved the exposure of CD rats (30/sex/group) to 0, 492, 2460 or 7380 mg/m^3 of the C9 fraction via inhalation for 6 hours/day, 5 days/week (Seed, 1989). Evidence of parental toxicity included reduced body weights, increased salivation, hunched posture, aggressive behaviour, and death. Reproductive toxicity was indicated by reduced litter size and reduced pup body weight. Both the reproductive and parental toxicity were observable at all dose levels tested and consequently, a Lowest-Observed-Effect-Level (LOEL) of 492 mg/m^3 was identified. Developmental toxicity, including possible neurotoxicity, was also

observed. The author noted abnormal gait, impaired hind limb function, tremors and lack of righting reflex in the rats exposed to the highest dose (7380 mg/m^3). No further details were available from the study concerning the developmental effects.

In another study conducted by the International Research and Development Corporation for the American Petroleum Institute, CD-1 mice (30/dose group) were exposed via inhalation to the C9 fraction at concentrations of 0, 492, 2460 or 7380 mg/m^3 for 6 hours/day during days 6-15 of gestation (Campbell, 1989). Based on the results of the study, the U.S. EPA concluded that there was evidence of developmental toxicity at all dose levels. The author noted increased frequency of whole litter resorptions, reduced pup viability and malformations (cleft palate, unossified sternebrae and reduced skull ossification). The author identified a LOEL of 492 mg/m^3 for the observed developmental effects.

3.4 Genotoxicity and Mutagenicity

No information regarding the genotoxicity or mutagenicity of trimethylbenzenes was identified in the available scientific literature and only limited data is available on the genotoxicity and mutagenicity of the C9 aromatic fraction. Results indicate that the C9 fraction does not induce gene mutations in prokaryotes (*Salmonella typhimurium* / mammalian microsome assay); nor does it cause chromosomal aberrations or sister chromatid exchange in mammalian cells in culture (*i.e.*, Chinese hamster ovary cells with and without metabolic activation) (U.S. EPA, 1994). In addition, the C9 fraction was found to cause no chromosome aberrations in the bone marrow of Sprague-Dawley rats exposed by inhalation (6 hours/day for 5 days) (U.S. EPA, 1994). In 1998, genotoxicity endpoints for trimethylbenzene isomers (1,2,3-TMB; 1,2,4-TMB; and 1,3,5-TMB) were studied at the Nofer Institute of Occupational Medicine. Results indicated that only the 1,2,3-TMB isomer had a mutagenic effect on *S. typhimurium*, though all three compounds were observed to have a cytogenetic potential of increasing the sister chromatid exchanges in these cells. However, the data provided limited evidence for the genotoxic activity of 1,2,3-TMB and inadequate evidence for the genotoxic activity of 1,2,4-TMB and 1,3,5-TMB (Janik-Spiechowicz *et al.*, 1998).

3.5 Carcinogenicity

No inhalation studies regarding the carcinogenicity of 1,2,4-TMB in humans or animals were identified in the available scientific literature. Only one animal carcinogenicity study was identified (Maltoni *et al.,* 1997), involving exposure to 1,2,4-TMB by oral gavage. The study reported a slight increase in total malignant tumours in both sexes of Sprague-Dawley rats exposed to a single dose of 800 mg/kg body weight/day of 1,2,4-TMB by stomach tube for 4 days/week for 104 weeks. In the male rats, an increased incidence of head cancers, including cancers identified in the zymbal gland, ear duct

and nasal and oral cavity was observed. The predominant type of head cancer identified was neuroesthesioepithelioma, which is normally rare in Sprague-Dawley rats.

Presently, the International Agency for Research on Cancer (IARC), the U.S. EPA and the American Conference of Governmental Industrial Hygienists (ACGIH) have not classified trimethylbenzene mixture or any trimethylbenzene isomer as to its carcinogenicity.

3.6 Environmental Effects

The environmental impacts associated with TMB isomers in ambient air are not expected to be a significant contributing factor during the development of air standards. Chemical and physical properties of the three isomers are similar to each other, as summarized by the ACGIH (ACGIH, 2001). As such, the environmental effects for 1,2,3-TMB and 1,3,5-TMB is expected to be similar to 1,2,4-TMB summarized below.

1,2,4-TMB will not persist long in the air due to rapid degradation and is not expected to partition substantially to soil or surface water. Most anthropogenic emissions of 1,2,4-TMB are expected to dissipate quickly from the environment.

No information was found concerning the toxicity of 1,2,4-TMB to terrestrial plants. However, due to the high volatility of the chemical, it is unlikely to accumulate in soil to levels that are expected to be toxic to plants (U.S. EPA, 1994a).

In aquatic organisms, slight to moderate toxicity of 1,2,4-TMB has been observed. Toxicity tests indicated a 96-hour LC_{50} of 57 mg/L for fathead minnows (Geiger *et al*., 1986) and a 48-hour EC_{50} (intoxication-immobility) of 3.6 mg/L for the crustacean *Daphnia magna* (Bobra *et al*., 1983). Bioconcentration factors (BCFs) in aquatic organisms include values of 31 to 275, measured in carp (CITI, 1992), 132 measured in fish (Park and Lee, 1993) and an estimated BCF of 432 (HSDB, 2002). Environment Canada (1995), as cited in the Canadian Environmental Protection Act (CEPA) Environmental Emergencies Planning Provisions data gathering guidelines, considers this range of BCFs to represent a slight to moderate bioconcentration in aquatic organisms.

Due to the rapid loss of 1,2,4-TMB from soil and water by volatilization and biodegradation, it is unlikely that it will be accumulated to any significant degree in terrestrial or aquatic organisms. In addition, it has low to moderate ecotoxicity and is therefore unlikely to have a significant impact on ecological receptors at a level that is protective of human health.

4.0 Review of Existing Air Quality Criteria

4.1 Overview

Currently in Ontario, the 24-hour Ambient Air Quality Criterion (AAQC) and the half-hour Point of Impingement (POI) values for 1,2,4-TMB are 1000 µg/m^3 and 500 µg/m^3, respectively. The 24-hour AAQC is based on odour and health considerations, while the half-hour value is based on odour.

In revising the air quality standards for Ontario, the Ministry of the Environment is considering risk assessments and standards and guidelines used by environmental agencies world-wide. This report reviews the scientific basis for air quality guidelines and standards developed for trimethylbenzenes by the States of Michigan, New York, and Texas. No environmental standards were found for TMBs for the Canadian Federal Government, the U.S. EPA, the States of California, Massachusetts and North Carolina or for the Netherlands, Sweden, the United Kingdom and the World Health Organization. Agency specific summaries of guideline information for all TMB isomers are presented in Section 10.0, the Appendix of this report. A brief summary is presented in Table 1.

Table 1: Summary of Existing Air Quality Guidelines[1] for Trimethylbenzenes (individual isomers and mixed isomers)

Agency	Guideline Value	Basis of Guideline	Date[2]	Comments
Canada (CEPA)	No guideline listed.			Not on the Priority Substances Lists (PSL1 or PSL2)
Ontario (MOE)	1000 µg/m^3 (24-hour AAQC) *	Odour and Health	1988	Ambient Air Quality Criterion
Limit applied to 1,2,4-TMB only	500 µg/m^3 (Half -hour, POI) *	Odour	1988	Point of Impingement
U.S. EPA (IRIS)	No guideline listed.			
California (OEHHA)	No guideline listed.			
Massachusetts (DEP)	No guideline listed.			
Michigan (DEQ)	1230 µg/m^3 (8-hr ITSL) **	Derived based on the ACGIH's TLV-TWA of 25 ppm (123 mg/m^3)	1996	The combined ambient impact of all trimethylbenzene isomers cannot exceed the ITSL of 1230 µg/m^3 Initial Threshold Screening Level.
New York (DEC)	290 µg/m^3 (AGC) **	Derived based on the ACGIH's TLV-TWA of 25 ppm (123 mg/m^3) for TMB (mixed isomers)	2000	Annual Guideline Concentration.
North Carolina (DENR)	No guideline listed.			
Texas (CEQ)	1250 µg/m^3 (1-hour ESL) **	Derived based on the ACGIH's TLV-TWA of 25 ppm (123 mg/m^3) for TMB (mixed isomers)	1994	Effects Screening Level
	125 µg/m^3 (annual ESL) **	Derived based on the ACGIH's TLV-TWA of 25 ppm (123 mg/m^3) for TMB (mixed isomers)	1994	Effects Screening Level
The Netherlands	No guideline listed.			
Sweden	No guideline listed.			
United Kingdom	No guideline listed.			

Agency	Guideline Value	Basis of Guideline	Date[2]	Comments
WHO (PHE & Europe)	No guideline listed.			

* Agency has listed the reported limit for 1,2,4-Trimethylbenzene only
**Agency has listed the reported limit for 1,2,3-/1,2,4-/1,3,5-Trimethylbenzene and Trimethylbenzene (mixed isomers)

1. Guidelines in this table can refer to: guidelines, risk-specific concentrations based on cancer potencies, and non-cancer-based reference concentrations.
2. Date here refers to when the health-based guideline background report or original legislative initiative was issued. The sources were the respective agency documents.

In reviewing the air quality guidelines and exposure limits presented in Table 1, it should be noted that the Ministry of the Environment typically uses a factor of **15** to convert from guidelines based on annual average concentrations to half-hour point-of-impingement limits and a factor of **3** to convert from guidelines based on 24-hour average concentrations. These factors are derived from empirical measurements and are selected to ensure that if the short-term limit is met, air quality guidelines based on longer-term exposures will not be exceeded. However, depending on the health end-point being considered, other conversion factors may also be employed.

Michigan, Texas and New York based their air standards, guidelines, or criteria on the ACGIH TLV-TWA value of 25 ppm (123 mg/m^3) for mixed trimethylbenzene isomers (CAS no. 25551-13-7).

Michigan's 8-hour Initial Threshold Screening Level (ITSL) of 1230 µg/m^3 was derived by dividing the ACGIH TLV-TWA by an uncertainty factor of 10 to protect sensitive subpopulations and another factor of 10 to account for the intermittent nature of occupational exposure compared to a continuous lifetime exposure (Sills, 2000).

New York's AGC of 290 µg/m^3 was derived by dividing the ACGIH TLV-TWA by a factor of 4.2 to account for the intermittent nature of occupational exposure compared to a continuous lifetime exposure, followed by the application of an uncertainty factor of 100 (DeSantis, 2000).

The State of Texas derived a 1-hour and an annual Effects Screening Levels (ESL) of 1250 µg/m^3 and 125 µg/m^3, respectively. Texas employed the value of 125 mg/m^3 to derive the ESL values. This difference from the ACGIH TLV-TWA of 123 mg/m^3 is due to slight differences in rounding by Texas during the conversion between 25 ppm to mg/m^3. Both the 1-hour and annual ESL values were derived by dividing the ACGIH TLV-TWA of ≈125 mg/m^3 by the uncertainty factors 100 and 1000, respectively. Uncertainty factors applied to both the 1-hour and annual limit accounted for sensitive individuals in a population and a conversion from intermittent to continuous exposure. Texas generally applies an additional factor of 10 to the 1-hour ESL to obtain the annual limit (Lee, 2004).

Based on the reported CNS and hematological effects, as well as the development of asthmatic bronchitis in painters exposed to solvents containing mixed isomers of TMB (Battig *et al.,* 1956), the ACGIH derived their Threshold Limit Value, Time-Weighted Average (TLV-TWA) of 123 mg/m^3 for both the individual isomers of trimethylbenzene and any combination thereof (ACGIH, 2002a,b).

4.2 Evaluation of Existing Criteria

None of the regulatory agencies reviewed have derived their air quality criteria directly from trimethylbenzene experimental data. The TLV-TWA derived by the ACGIH is the basis of all the available air quality criteria.

The principal study used by the ACGIH is the only identified human epidemiological study available on trimethylbenzenes. The ACGIH's TLV-TWA value of 123 mg/m^3 was based on the study of Battig *et al*. (1956), which identified a LOAEL of 295 mg/m^3 for the observed CNS and hematological effects, as well as the development of bronchitis.

There are several challenges to using the Battig *et al*. (1956) study which were not addressed in the ACGIH write-up for the TLV-TWA value. This study is a 1956 German publication which could not be obtained for further evaluation. The chemicals the employees were exposed to were a mixture of TMB isomers and other compounds. Further studies on TMB have failed to produce any hematological effects at the concentrations the workers were exposed to. Gerarde (1960) noted that the concomitant exposure to benzene was likely the cause of the observed hematological effects. Animal studies which have studied benzene exposure have provided support for the observed hematological effects observed in humans, as several chronic studies have reported effects such as decreased erythrocytes and increased leukocytes (Bernshtein, 1972). Other challenges in using this study include that there is an unspecified exposure period for the 27 employees; and the method of how the CNS effects were quantified could not be identified.

Finally, the potential for eye, nose and respiratory irritation with acute exposure to trimethylbenzenes has not been addressed in the ACGIH TLV-TWA value.

5.0 Responses of Stakeholders to the Information Draft

In August 2005, the Ministry posted Information Draft documents for twelve chemicals, including 1,2,4-TMB, for air standards development under the Standards Plan (MOEE, 1996; MOE, 1999) to the Environmental Registry. The Ministry requested input regarding: the completeness of relevant inhalation toxicological information for 1,2,4-TMB examined by the Ministry; if there was any relevant and critical information not reviewed which may influence the development of air quality standards for any of the individual TMB isomers and any mixture of the isomers; and if the study by Battig *et al.* (1956) study ignored acute effects.

During the consultation period the Ministry received 1 submission from a stakeholder regarding the draft document for 1,2,4-TMB.

The stakeholder pointed out that a more sensitive endpoint may be identified considering recent animal studies which report pulmonary lesions, long-term CNS effects and developmental effects occurring around the concentration identified from the Battig *et al.* (1956) study.

6.0 Responses of Stakeholders to the Rationale Document

In June, 2006, the Ministry posted to the Environmental Registry a document titled "Rationale for the Development of Ontario Air Standards for Trimethylbenzenes" and requested public comments over a period of 91 days. The Ministry received comments from six stakeholders. Highlights from these comments are summarized below.

Comments Specific to Trimethylbenzene:

Comment: The U.S. EPA Region 9 has developed a 'preliminary remediation goal' (PRG) for inhalation exposure to 1,2,4-TMB based on route to route extrapolation from an oral reference dose. It is not discussed in the rationale document.

Response: PRGs are derived screening levels used in the U.S. EPA Superfund project as initial cleanup goals. When a PRG is exceeded, further evaluation of the potential risk that may be posed by the site contaminant may be appropriate. PRGs are derived from standardized equations combining exposure information assumption with U.S. EPA toxicity data. All PRGs are considered by the U.S. EPA to be protective for humans over a lifetime exposure.

Region 9 has a PRG of 6.2 µg/m^3 for both 1,2,4-trimethylbenzene and 1,3,5-trimethylbenzene. These values were obtained using an inhalation Reference Dose of 0.0017 mg/kg-d. This inhalation reference dose is from a provisional peer reviewed toxicity value from the U.S. EPA. The information to support this reference dose could not be obtained, therefore it could not be confirmed that the study used to derive the provisional peer reviewed toxicity value is an inhalation study or an oral study. For this reason the PRGs will not be discussed in this document.

Comment: An explanation was requested as to why the toxicological endpoint of CNS effects was chosen as the bases for the Ministry air standard, and not the possible respiratory effects observed in the Korsak *et al*. 2000 (a,b) literature.

Response: There are 7 recent inhalation studies available on trimethylbenzene isomers which used similar dosing regimes, the same species and the same method of exposure. Endpoints which were investigated included CNS effects, hematological effects, clinical pathology and histopathology. Together they include over 40 different tests. Five studies investigated the potential CNS effects and 2 studies investigated the potential hematological effects, clinical pathology and histopathology. Of these potential endpoints, various effects were observed at all dosages (123 mg/m^3, 492 mg/m^3, and 1230 mg/m^3), and these effects varied in strength according to type of isomer used and dosage used. Only 2 studies (CNS studies) observed significant adverse effects at 123 mg/m^3. These observations could not be repeated in other studies, or were inconsistent with effects observed in other studies, and were very mild in nature. The Ministry focused on CNS effect as a critical endpoint for TMB, as the respiratory effect observed at 492 mg/m^3 was very mild in nature compared to the observed CNS effects. There are also more studies on TMB which focus on CNS effects, and similar chemicals, such as toluene, also have CNS effects as a critical endpoint.

Comment: The uncertainty factor of 3 ($10^{½}$) used to extrapolate from the CNS LOAEL of 492 mg/m^3 to a NOAEL in the MOE rationale document results in a value that exceeds the stated NOAEL of 123 mg/m^3 in the Korsak *et al*. 2000 (a,b) respiratory studies. An explanation as to why an uncertainty factor of 3 ($10^{½}$) used in the rationale was requested.

Response: In reviewing the toxicological information available in the 7 inhalation studies (mentioned in above comment), the Ministry has revised its standard. The basis for the standard is still CNS effects, however the NOAEL of 123 mg/m^3 was used as a point of departure, as such eliminating the uncertainty factor of 3 ($10^{½}$). See section 7.0 for further detail.

It should be noted that there is not a considerable difference between the standards derived using the point of departure (POD) of 492 mg/m^3 or 123 mg/m^3. The severity of the effects observed at 492 mg/m^3 in either the respiratory or CNS studies was low. In addition, based on the studies available, the LOAEL appears to be close to the NOAEL.

Both of these factors lend support to using a lower uncertainty factor of 3 ($10^{½}$) to adjust from a LOAEL to a NOAEL (as done in the previous rationale).

However, to reduce uncertainty, it is appropriate to use the NOAEL of 123 mg/m^3 as a POD. For this reason, the Ministry will be changing the rationale, and the new 24-hour AAQC will be 220 µg/m^3.

Comment: A rationale should be provided in the Ministry's Decision Document as to why a Human Equivalent Concentration (HEC) was not calculated in the development of the 24-hour air standard.

Response: As discussed above, the MOE considers the critical endpoint for trimethylbenzenes to be potential CNS effects. Trimethylbenzenes fit the description of a Category 3 gas, according to the U.S. EPA (1994c). Gases or vapors in Category 3 are relatively water insoluble and unreactive in the extrathoracic and tracheobronchial regions of the lung. Category 3 gases typically result in insignificant toxicity to the lung, although some respiratory tract toxicity may be related to recirculation. The uptake of these gases is predominantly in the pulmonary region and is perfusion limited. The site of toxicity is generally remote to the principal site of absorption.

In general, the $NOAEL_{HEC} = NOAEL_{adj} \times RGDR$ where:

$NOAEL_{HEC}$ Human Equivalent No-Observed-Adverse-Effect-Level

$NOAEL_{adj}$ Animal No-Observed-Adverse-Effect-Level, adjusted for continuous exposure

RGDR Regional Gas Dose Ratio

The following formula describes the calculation of the Regional Gas Dose Ratio (RGDR) used in HEC calculations for Category 3 gases.

$RGDR = (H_{b/g})_A / (H_{b/g})_H$ where:

$(H_{b/g})_A$ Animal blood:air partition coefficient

$(H_{b/g})_H$ Human blood:air partition coefficient

The human blood:air partition coefficient was reported at 66.5 for 1,2,3-TMB, 59.1 for 1,2,4-TMB and 43.0 for 1,3,5-TMB (Jarnberg, 1995). Partition coefficients change with each isomer of TMB. As the Ministry is creating a standard for all trimethylbenzene isomers it was inappropriate to choose a particular blood:air partition coefficient. As such, a RGDR could not be obtained and a HEC calculation was not performed.

Comment: It was suggested that the lack of data for reproductive and developmental toxicity and carcinogenicity for trimethylbenzenes warrants the use of an additional uncertainty factor.

Response: The information available in the rationale document for reproductive and development toxicity was considered sufficient by the Ministry as one study was available for 1,2,4-TMB and 1,3,5-TMB, and two additional reproductive and multigenerational studies were available on the petroleum refinery distillation fraction known as the C9 aromatic hydrocarbon fraction. 1,2,4-TMB has been reported as a major constituent (roughly 40 percent) of this fraction. These studies did not indicate that reproductive or developmental toxicity may occur at a lower concentration than the NOAEL of 123 mg/m^3. The Ministry is satisfied with the information available, and does not deem that an additional uncertainty factor is warranted.

The information available in the rationale document for carcinogenicity was also considered sufficient. There is one chronic study on 1,2,4-TMB available which did not indicate that carcinogenic effects occur at a lower concentration than the NOAEL of 123 mg/m^3. In addition, similar compounds which have exhibited similar CNS effects observed withTMB (such as toluene and xylene) have not been classified as a carcinogen by the Ministry or other major agencies. The Ministry is satisfied with the information available, and does not deem that an additional uncertainty factor is warranted.

Comment: The new Ministry ½-hour standard may not adequately incorporate odour considerations as it is larger than the previous POI guideline for 1,2,4-trimethylbenzene, which is based on odour considerations.

Response: The previous POI guideline of 500 µg/m^3 for 1,2,4-trimethylbenzene was based on odour thresholds for related substances, such as cumene, xylene and toluene (Verschueren, 1983). New scientific information is available on the odour thresholds of trimethylbenzenes. The odour threshold of 2.4 ppm (12,000 µg/m^3) was identified for 1,2,4-trimethylbenzene and 2.2 ppm (10,700 µg/m^3) was identified for 1,3,5-trimethylbenzene (AIHA, 1989). As the odour thresholds were significantly higher than the POI guideline, the odour based POI guideline was no longer appropriate. As such, a health based ½ -hour standard was derived, which took into consideration potential odour concerns.

General Comments:

In addition to technical comments on this specific substance, MOE received ‘general’ comments related to the standard setting process, implementation of standards and odour issues. Some of these comments formed part of the response to the Rationale Documents, which were posted from June 26, 2006 to September 25, 2006. Other comments were in response to the *"Proposal to amend Ontario Regulation 419/05: Air*

Pollution-Local Air Quality" posted from June 15 to September 25, 2006, with a subsequent posting April 7, 2007 to May 7, 2007 of the proposed draft amendments to O. Reg. 419/05. With the June to September, 2006 posting the MOE also introduced a *"Proposed Approach for the Implementation of Odour-Based Standards and Guidelines"* to which it also received comments.

A detailed summary of these general comments and MOE's responses to them can be found in the following two related postings:

1) EBR #: 010-0000 – Proposal to Amend Ontario Regulation 419/05:Air Pollution-Local Air Quality under the Environmental Protection Act; and

2) EBR #: RA06E0006 – Proposed Approach for the Implementation of Odour-Based Standards and Guidelines.

7.0 Considerations in the Development of an Ambient Air Quality Criterion for Trimethylbenzene isomers (individuals and mixed isomers)

Currently in Ontario, the 24-hour Ambient Air Quality Criterion (AAQC) and the half-hour Point of Impingement (POI) values for 1,2,4-TMB are 1000 µg/m^3 and 500 µg/m^3, respectively. The 24-hour AAQC is based on odour and health considerations, while the half-hour value is based on odour considerations.

Under most environmental exposure conditions, inhalation exposure to TMB would likely occur as a mixture of all three isomers. The physical and chemical properties and toxicological endpoints are similar for all TMB isomers. Exposures to individual TMB isomers would be expected to occur rarely, and would likely be restricted to unique occupational or experimental situations. Therefore, the MOE is expanding the current AAQC and POI value to include all isomers of trimethylbenzene and to any mixtures of these isomers.

Trimethylbenzenes appear to be readily absorbed from the lungs. Once in the bloodstream TMB is primarily bound to red blood cells, and upon distribution within the body, accumulates in fatty tissues, as is expected based on its lipophilicity. Metabolism

of the TMB isomers in humans and animals occurs by side-chain oxidation to form alcohols and carboxylic acids or hydroxylation to phenols, which are then conjugated with glucuronic acid, glycine, or sulphates prior to urinary excretion. Dimethylbenzoic acids are the main excreted metabolite of absorbed trimethylbenzenes as urinary excretion of these metabolites correlated well with the absorbed.

None of the regulatory agencies reviewed have derived their air quality criteria directly from trimethylbenzene experimental data. In addition, none of the regulatory agencies have reviewed/updated their TMB air quality criteria since the recent toxicological information for TMB has become available. The TLV-TWA derived by the ACGIH is the basis of all the available air quality criteria. The ACGIH's TLV-TWA value of 123 mg/m^3 was based on the study of Battig *et al*. (1956), which reports CNS and hematological effects in humans exposed to trimethylbenzene vapours concentrations up to 60 ppm (295 mg/m^3). There are several challenges to using the Battig *et al.* (1956) study for developing an air standard. Some unknowns associated with the study include the following: workers were exposed to a mixture of compounds, including benzene; 27 workers were exposed to this mixture for an unspecified amount of time; and method of quantifying the CNS effects could not be identified as the original study could not be obtained.

Isomers of TMB have been described as irritants with a potential to cause eye, nose and respiratory irritation. The development of bronchitis following chronic exposure in the Battig *et al*. (1956) study is likely the result of constant respiratory irritation and therefore, the potential for acute irritation effects may also need to be considered in the development of an air quality criterion. Sensory irritation was quantified by measurements of the respiratory rate in mice. Korsak *et al.* (1997) suggests that the depression of the respiratory rate (RD) in mice correlates with the extent of eye and respiratory irritation in man. From this study, an occupational limit for trimethylbenzenes based on RD_{50} values was suggested to be between 10 to 30 ppm. This is comparable to the current ACGIH TLV-TWA of 25 ppm and therefore likely protective for irritative effects. In a human toxicokinetic study volunteers were exposed to 11 mg/m^3 of 1,2,4-TMB. There were no reports of irritation in this study.

Several subchronic rat studies (Korsak and Rydzynski, 1996; Gralewicz *et al*., 1997; Wiaderna *et al.*, 1998; Gralewicz and Wiaderna, 2001; and Wiaderna *et al.* 2002) examined the potential CNS effects associated with inhalation exposure to trimethylbenzenes. Behavioural effects were measured to assess potential CNS effects. 1,2,3-TMB varied in the specific behaviour effects observed and the reported concentration at which these effects were noted. Different behavioural effects were produced at 123 mg/m^3 and 492 mg/m^3 (Korsak and Rydzynski, 1996; Wiaderna *et al.*, 1998). 1,2,4-TMB produced similar behavioural effects are 492 mg/m^3 (Gralewicz, 1997; Gralewicz and Wiaderna, 2001), and 1,3,5-TMB produced behavioural effects (decreased pain sensitivity) at 492 mg/m^3 (Gralewicz and Wiaderna, 2001; Wiaderna *et al.*, 2002). Overall, this series of studies concluded that long-term CNS effects may

follow a 4-week inhalation exposure to any of the TMB isomers at concentration as low as 492 mg/m^3. The weight of evidence upon reviewing these studies supports a NOAEL of 123 mg/m^3 for trimethylbenzenes.

In more recent subchronic inhalation studies by Korsak *et al*. (2000a, 2000b), rats were exposed to either 1,2,4-TMB or 1,2,3-TMB, however, effects other than neurotoxicity were also examined. Korsak *et al.* (2000a, 2000b) reported an overall low degree of systemic toxicity associated with exposure to 1,2,3-TMB and 1,2,4-TMB. Proliferation of peribronchial lymphatic tissue and interstitial lymphocytic infiltration were observed in the male and female rats exposed to 492 and 1230 mg/m^3 of 1,2,4-TMB (Korsak *et al.* 2000a). Proliferation of the peribronchial lymphatic tissue, formation of lymphoepithelium in the bronchi, an increased number of goblet cells and interstitial lung parenchyma infiltrations was observed at 1230 mg/m^3 following exposure to 1,2,3-TMB (Korsak *et al.* 2000b). Both studies report a NOEL of 123 mg/m^3 for male and female rats and pathological changes in the lower respiratory system. The respiratory effect observed in these studies at 492 mg/m^3 were very mild in nature compared to the CNS effects observed in the 5 studies discussed above. As such, the respiratory effects are not considered the critical endpoint for trimethylbenzenes.

The only study identified, which investigates the reproductive and developmental toxicity of trimethylbenzenes, reported a NOAEL for prenatal developmental toxicity and this was identified at 300 ppm (1476 mg/m^3) for 1,2,4-TMB and 1,3,5-TMB. It should be noted that maternal toxicity, as defined by a significant decrease in body weight gain and food consumption, was also identified at 300 ppm for 1,3,5-TMB (Saillenfait *et al.*, 2005).

There is one chronic study on 1,2,4-TMB available which did not indicate carcinogenic effects occur at a lower concentration then the NOAEL of 123 mg/m^3. In addition, similar compounds which have exhibited similar CNS effects observed in TMB (such as toluene and xylene) have not been assessed as a carcinogen by the Ministry or other major agencies.

CNS effects were chosen as the critical effect since CNS effects were observed in 5 subchronic inhalation studies, and CNS effects were also chosen as the critical endpoint in very similar compounds, such as toluene and xylene. In addition, there is a reasonable amount of toxicological information to support the CNS effects observed in rats following TMB exposure. In critically reviewing Korsak and Rydzynski (1996), Gralewicz *et al.* (1997), Wiaderna *et al.* (1998), Gralewicz and Wiaderna (2001), and Wiaderna *et al.* (2002), a NOAEL of 123 mg/m^3 and a LOAEL of 492 mg/m^3 was identified for TMB.

An AAQC can be derived based on the data from 5 subchronic inhalation studies which indicate 123 mg/m^3 as a possible NOAEL for CNS effects among all TMB isomers.

To convert the NOAEL to continuous exposure ($NOAEL_{adj}$):

All 5 supporting studies exposed rats to TMB vapours 6 hour/day, 5 days/week

$NOAEL_{adj}$ = 123 mg/m^3 x 6 hours/24 hours x 5 days/7 days
= 22.0 mg/m^3
= 22,000 µg/m^3

A cumulative uncertainty factor of 100 is applied to the $NOAEL_{adj}$ to derive the 24-hour standard of 220 µg/m^3. The uncertainty factor of 100 incorporates a factor of 3 ($10^{½}$) for interspecies extrapolation, a factor of 10 for intraspecies variability and a factor of 3 ($10^{½}$) for subchronic to chronic extrapolation. This value protects for both CNS effects and respiratory irritation.

A factor of 3 ($10^{½}$) was considered sufficient for interspecies extrapolations. Animal and human toxicity data suggest that TMB and the different TMB isomers produce similar effect around the same exposure concentrations. A factor of 10 was considered sufficient for intraspecies variability to account for variations in susceptibility within the human population. Finally, a factor of 3 ($10^{½}$) was considered sufficient to extrapolate from subchronic to chronic as the studies identified covered observations for 3 months of the rat's 2 year lifetime expectancy.

8.0 Decision

The Ministry of the Environment has reviewed and considered air quality guidelines and standards used by leading agencies worldwide. After reviewing additional toxicological information, the Ministry considers a series of subchronic inhalation rat studies which identify CNS effects to be the most appropriate basis for the derivation of health-based air standards for trimethylbenzenes.

The Ministry of the Environment uses a factor of **3** to convert from criteria based on 24-hour average concentrations to half-hour POI standards. This factor is derived from empirical measurements and is selected to ensure that if the short-term limit is met, air quality standards based on longer-term exposures will not be exceeded (MOE, 1987; MOEE, 1994).

Based on an evaluation of the scientific rationale of air guidelines from leading agencies, an examination of current toxicological research, and comments from stakeholders, the following Air Quality Standards are set for trimethylbenzenes:

- **A 24-hour average AAQC of 220 $\mu g/m^3$ (micrograms per cubic metre of air) for trimethylbenzenes* based on the adverse CNS effects of these compounds; and**

- **A half-hour standard of 660 $\mu g/m^3$ (micrograms per cubic metre of air) for trimethylbenzenes* based on the adverse CNS effects of these compounds.**

* Note: The AAQC and half-hour POI standard will apply to any isomer of trimethylbenzene (i.e., 1,2,3-TMB (CAS# 526-73-8) or 1,2,4-TMB (CAS# 95-63-6) or 1,3,5-TMB (CAS#108-67-8)) or to any mixture of these isomers.

These effects-based AAQCs and the corresponding effects-based half hour standards will be incorporated as standards into Ontario Regulation 419/05: Air Pollution – Local Air Quality (O. Reg. 419/05). The AAQCs will be incorporated into Schedule 3 of O. Reg. 419/05; the half-hour standard will be incorporated into Schedule 2.

MOE generally proposes a phase-in period for new standards or standards that will be more stringent than the current standard or guideline. The phase-in for this compound is as set out in O. Reg. 419/05.

Among other things, O. Reg. 419/05 sets out the applicability of standards and appropriate averaging times, phase-in periods, types of air dispersion models and when various sectors are to use these models. There are 3 guidelines that support O. Reg. 419/05. These guidelines are:

- "Guideline for the Implementation of Air Standards in Ontario" (GIASO);

- "Air Dispersion Modelling Guideline for Ontario" (ADMGO); and

- "Procedure for Preparing an Emission Summary and Dispersion Modelling Report" (ESDM Procedure).

GIASO outlines a risk-based decision making process to set site specific alternative air standards to deal with implementation barriers (time, technology and economics) associated with the introduction of new/updated air standards and new models. The alternative standard setting process is set out in section 32 of O. Reg. 419/05.

For further information on these guidelines and O. Reg. 419/05, please see the Ministry's website http://www.ontario.ca/environment and follow the links to local air quality.

9.0 References

ACGIH. 2002a. Documentation of the threshold limit values and biological exposure indices. Sixth Edition. American Conference of Governmental Industrial Hygienists (ACGIH) Inc., Cincinnati, OH.

ACGIH. 2002b. Guide to occupational exposure values – 2002. Compiled by the American Conference of Governmental Industrial Hygienists (ACGIH) Inc., Cincinnati, OH.

Acton, D.W. and Barker, J.F. 1992. In situ biodegradation potential of aromatic hydrocarbons in anaerobic groundwaters. *J Contam Hydrol* **9**: 325-52. Cited In: HSDB, 2002.

AIHA (American Industrial Hygiene Association). 1989. Odor thresholds for chemicals with established occupational health standards. American Industrial Hygiene Association, Akron, OH.

AQUIRE. 1994. EPA ERL-Duluth's Aquatic Ecotoxicology Data System. U.S. EPA, Duluth, MN. Retrieved August 1994. Cited In: U.S. EPA, 1994a.

Atkinson, R. and Carter, W.P.L. 1984. Kinetics and mechanisms of gas-phase reactions of ozone with organic compounds under atmospheric conditions. *Chem Rev* **84**: 437-470.

Atkinson, R. 1989. *J Phys Chem Ref Data*. Monograph No. 1. Cited In: HSDB, 2002.

Atkinson, R. 1995. Gas-phase tropospheric chemistry of organic compounds. *J Phys Chem Ref Data.* Monogram **2**. 1-216. Cited In: CalARB, 1997a.

Battig, K., Grandjean, E., Rossi, L. and Rickenbacher, J. 1958. Toxicological investigations concerning trimethyl benzene. *Arch Gewerbepath Gewerbehyg* **16**:555-566. Cited In: ACGIH, 2002a.

Battig, K., Grandjean, E., and Turrian, V. 1956. Health damage after continuous exposure to trimethyl benzene in a painting workshop. *Z. Prev. Med*. **1**:389-403. Cited In: ACGIH, 2002a.

Bernshtein, L.M. 1972. *Vopr Gig Tr Profzabol Mater Nauch Konf* **53**. Cited In: Cavender, 1994.

Bertsch, W., Chang, R.C. and Zlatkis, A. 1974. The determination of organic volatiles in air pollution studies: characterization of profiles. *J Chromatogr Sci* **12(4)**:175-182. Cited In: Clayton and Clayton, 1994.

Bidleman, T.F. 1988. *Environ Sci Technol* **22**: 361-367. Cited In: HSDB, 2002.

Bingham, E., Cohrssen, B. and Powell, C.H. (Editors). 2001. Patty's Toxicology 5th edition; Hydrocarbons, Organic Nitrogen Compounds, Volume 4. John Wiley & Sons, Inc., Toronto, Canada.

Bobra, A.M., Shiu, W.Y. and Mackay. D. 1983. A predictive correlation for the acute toxicity of hydrocarbons and chlorinated hydrocarbons to the water flea (*Daphnia magna*). *Chemosphere* **12(9-10)**:1121-1129.

Brenniman, G., Hartung, R. and W.J. Weber Jr. 1976. A continuous flow bioassay method to evaluate the effects of outboard motor exhausts and selected aromatic toxicants on fish. *Water Res* **10(2)**:165-169. Cited In: Cavender, 1994.

Browning, E. 1965. Toxicity and Metabolism of Industrial Solvents. Elsevier Publishing Company. Amsterdam, Netherlands.

Budavari, S., O'Neill, M.J., Smith, A., Heckelman, P.A. and Kinneary, J.F. eds. 1996. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 12th Ed. Merck & Co., Inc. Whitehouse Station, N.J.

Budavari, S. eds. 1989. The Merck Index. 11th Ed. Merck & Co., Inc. Rahway, N.J. Cited In: CalARB, 1997a.

CalARB. 1995. Personal communication from Jim Shikiya, Monitoring and Laboratory Division to Kitty Martin, Stationary Source Division. Data from the ARB Surveillance Vehicle Program. Air Resources Board. Sacremento, CA. Cited In: CalARB, 1997a.

CalARB. 1997a. Toxic air contaminant identification list (summaries). California Environmental Protection Agency. Air Resources Board. Sacremento, CA.

CalARB. 1997b. Data retrieved from ATEDS (Air Toxics Emission Data System). Run date: July 11, 1997. Technical Support Division, Special Pollutants Emission Inventory Section. Sacremento, CA. Cited In: CalARB, 1997a.

Cameron, G.R., Paterson, J.L.H, DeSarain, G.S.W. and Thomas, J.C. 1938. The toxicity of some methyl derivation of benzene with special reference to pseudocumene and heavy coal tar naphtha. *J Pathol Bacteriol* **46**:95-107. Cited In: ACGIH, 2002a.

Campbell. 1989. Detailed review of C9 aromatic hydrocarbons. Memorandum from M. Campbell, Toxics Effects Branch to C. Auer, Health and Environmental Review Division, Office of Toxic Substances, U.S. EPA. Washington, D.C. Cited In: U.S. EPA, 1994a

Carlier, P. *et al.* 1988. Risol Natl Lab Issrisoe-M-2630. Tropospheric NOx Chem-Gasphase Multiphase Aspects. Cited In: HSDB, 2002.

Cavender. 1994. Aromatic hydrocarbons. *In*: Patty's Industrial Hygiene and Toxicology. 4th Ed. Vol. 2B. G.D. Clayton and F.E. Clayton, Eds. John Wiley and Sons, New York.

Cerf, J., Potvin, M., and Laham, S. 1980. Acidic metabolites of pseudocumene in rabbit urine. *Arch Toxicol* **45**:93-100. Cited In: Kostrzewski *et al.*, 1997.

Chan, C., Ozkaynak, H., Spengler, J.D. and Sheldon, L. 1991. Driver exposure to volatile organic compounds, CO, ozone, and NO_2 under different driving conditions. *Environ Sci Technol* **25(5)**:964-972. Cited In: CalARB, 1997a.

CHEMFATE. 1994. Syracuse Research Corporation's Environmental Fate Data Bases, retrieved 8/5/94. Syracuse Research Corporation, Syracuse, NY. Cited In: U.S. EPA, 1994a.

Chemfinder. 2003. Trimethylbenzene. *In*: ChemFinder.com: Database and Internet Searching. Accessed: March, 2003. http://www.chemfinder.com

CITI (Chemicals Inspection and Testing Institute). 1992. Biodegradation and bioaccumulation data of existing chemicals based on the CSCL Japan. Japan Chemical Industry Ecology - Toxicology and Information Center. ISBN 4-89074-101-1.

Clayton, G.D. and Clayton, F.E. eds. 1994. Patty's Industrial Hygiene and Toxicology. Vol. II, Part B. Toxicology. 4th Ed. John Wiley and Sons, Inc., Toronto. 1304-1305, 1340.

Dahl, A.R., Damon, E.G., Mauderly, J.L., Rothenberg, S.J., Seiler, F.A. and McClellan, R.O. 1988. Uptake of 19 hydrocarbon vapors inhaled by F344 rats. *Fundam Appl Toxicol* **10:**262-269.

Dann, T. and Wang, D. 1989. Measurement of volatile organic compounds in the Greater Vancouver Regional District. Pollution Measurement Division, Environment Canada. PMD 89-15.

Dann, T. 2002. Personal communication. Head, Air Toxics Section, Environment Canada.

Dean-Ross, D. 1993. Fate of Jet Fuel JP-4 in Soil. *Bull Environ Contam Toxicol* **51**: 596-99. Cited In: HSDB, 2002.

DeSantis, S. 2000. Personal Communication. State of New York. Department of Environmental Conservation. March 1, 2000.

Dowty, B.J., Laseter, J.L. and Storer, J. 1976. The transplacental migration and accumulation in blood of volatile organic constituents. *Pediatr Res* **10(7)**:696-701. Cited In: Cavender, 1994.

Environment Canada, *Toxic Substances Management Policy*. Minister of Supply and Services Canada. Catalogue No. En 40-499/1-1995:5, 1995. ISBN 0-662-61860-2.

Fukaya, Y., Saito, I., Matsumoto, T., Takeuchi, Y. and Tokudome, S. 1994. Determination of 3,4-dimethylhippuric acid as a biological monitoring index for trimethylbenzene exposure in transfer printing workers. *Int Arch Occup Environ Health* **65(5)**:295-297.

Geiger, D.L., Poirier S.H., Brooke L.T. and Call, D.J., eds. 1986. Acute toxicities of organic chemicals to fathead minnows (*Pimephales Promelas*). Vol. III. Superior,Wisconsin: University of Wisconsin-Superior, 1986. 215. Cited in: HSDB, 2002.

Gerarde, H.W. 1960. Toxicology and biochemistry of aromatic hydrocarbons. pp. 181-199. Elsevier Publishing Co., New York. Cited in: ACGIH, 2002a.

Gralewicz, S., Wiaderna, D., Tomas, T. and Rydzynski, K. 1997. Behavioral changes following 4-week inhalation exposure to pseudocumene (1,2,4-trimethylbenzene) in the rat. *Neurotoxicol Teratol* **19(4)**:327-333.

Gralewicz, S. and Wiaderna, D. 2001. Behavioral effects following subacute inhalation exposure to m-xylene or trimethylbenzene in the rat: a comparative study. *Neurotoxicology* **22(1)**:79-89.

HSDB (Hazardous Substances Database). 2002. Trimethylbenzene. *In*: Hazardous Substances Data Bank. Toxicology Data Network System. National Library Of Medicine. Washington, D.C. http://sis.nlm.nih.gov/cgi-bin/sis/search

HSDB (Hazardous Substance Databas). 2005. Mesitylene. *In*: Hazardous Substances Data Bank. Toxicology Data Network System. National Library Of Medicine. Washington, D.C. http://sis.nlm.nih.gov/cgi-bin/sis/search

Huo, J.Z., Aldous, S., Campbell, K. and Davies, N. 1989. Distribution and metabolism of 1,2,4,-trimethylbenzene (pseudocumene) in the rat. *Xenobiotica* **19(2)**:161-170.

Hutchins, S.R. 1991. Biodegradation of monoaromatic hydrocarbons by aquifer microorganisms using oxygen, nitrite, or nitrous oxide as the terminal electron acceptor. *Appl Environ Microbiol* **57**: 2403-07. Cited In: HSDB, 2002.

Ichiba, M., Hama, H., Yukitake, S., Kubota, M., Kawasaki, S. and Tomokuni, K. 1992. Urinary excretion of 3,4-dimethylhippuric acid in workers exposed to 1,2,4-trimethylbenzene. *Int Arch Occup Environ Health* **64(5)**:325-327.

Janik-Spiechowicz, E., Wyszyanska, K. and DziubaEtowska, E. 1998. Genotoxicity evaluation of trimethylbenzenes. The Nofer Institute of Occupational Medicine. Lodz, Poland. *Mutat Res* **412(3)**:299-305.

Jarnberg, J. 1995. Toxicokinetics of Inhaled Trimethylbenzenes in Man. National Institute for Working Life. ISBN 91-7045-457-4. Found: http://www.niwl.se/ah/ah.htm

Jarnberg, J., and Johanson, G. 1999. Physiologically based modeling of 1,2,4-trimethylbenzene inhalation toxicokinetics. *J Toxicol Appl Pharm* **155**:203-214.

Jarnberg, J., Johanson, G and Lof, A. 1996. Toxicokinetics of inhaled trimethylbenzenes in man. *Toxicol Appl Pharmacol* **140(2)**:281-288.

Jarnberg, J., Johanson, G., Lof, A. and Stahlbom, B. 1998. Toxicokinetics of 1,2,4-trimethylbenzene in humans exposed to vapours of white spirit: comparison with exposure to 1,2,4-trimethylbenzene alone. *Arch Toxicol* **72**:483-491.

Jarnberg, J., Johanson, G., Lof, A. and Stahlbom, B. 1997. Inhalation toxicokinectics of 1,2,4-trimethylbenzene in volunteers: comparison between exposure to white spirit and 1,2,4-trimethylbenzene alone. *Sci Total Environ* **199(1-2)**:65-71.

Jarnberg, J., Stahlbon, B., Johanson, G. and Lof, A. 1997b. Urinary excretion of dimethylhippuric acids in humans after exposure to trimethylbenzenes. *Int Arch Occup Environ Health* **69(6)**:491-497.

Klaassen, C.D., Amdur, M.O. and Doull, J. 1991. eds. Casarett and Doull's Toxicology: The basic science of poisons. 5th Edition. McGraw-Hill, Toronto.

Korsak, Z., Swiercz and Rydzynski, K. 1995. Toxic effects of acute inhalation exposure to 1,2,4-trimethylbenzene (pseudocumene) in experimental animals. *Int J Occup Med Environ Health* **8(4)**:331-337.

Korsak, Z. and Rydzynski, K. 1996. Neurotoxic effects of acute and subchronic inhalation exposure to trimethylbenzene isomers (pseudocumene, mesitylene, hemimellitene) in rats. *J Occup Med Env Health* **9(4)**:341-349.

Korsak, A., Rydzynski, K. and Jajte, J. 1997. Respiratory irritative effects of trimethylbenzenes: An experimental animal study. *J Occup Med Env Health* **10(3)**:303-311.

Korsak, Z., Stetkiewicz, J., Majcherek, W., Stetkiewicz, I., Jajte, J. and Rydzynski, K. 2000a. Sub-chronic inhalation toxicity of 1,2,4-trimethylbenzene (pseudocumene) in rats. *Int J Occup Med Environ Health* **13(2)**:155-164.

Korsak, Z., Stetkiewics, J., Majcherek, W., Stetkiewicz, I., Jajte, J. and Rydzynski, K. 2000b. Subchronic inhalation toxicity of 1,2,3-trimethylbenzene (hemimellitene) in rats. *Int J Occup Med Environ Health* **13(3)**:223-232.

Kostrzewski, P., Wiaderna-Brycht, A. and Czerski, B. 1997. Biological monitoring of experimental human exposure to trimethylbenzene. *Sci Total Environ* **199 (1-2)**:73-81.

Lazarew, N.V. 1929. Toxicity of various hydrocarbon vapors. *Arch Exptl Pathol Pharmakol* **143**:223-239. Cited In: ACGIH, 2002a.

Lee, J. 2004. Personal Communication. State of Texas. Texas Commission on Environmental Quality. Email: August 6, 2004.

Lyman, W.J., W.R. Reehl and D.H. Rosenblatt. 1990. *In*: Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds. Washington, DC. Amer. Chem. Soc. Cited In: HSDS, 2002.Maltoni, C., Ciliberti, A. and Carretti, D. 1982. Experimental contributions in identifying brain potential carcinogens in the petrochemical industry. *Ann NY Acad Sci* **381**:216-249. Cited In: Beije, 1995.

Maltoni, C., Ciliberti, A., Pinto, C., Soffritti, M., Belpoggi, F. and Menarini, L. 1997. Results of long-term experimental carcinogenicity studies of the effects of gasoline, correlated fuels, and major gasoline aromatics on rats. *Ann NY Acad Sci* **837**:15-52.

Marion, C.V., Malaney, G.W. 1964. Proc 18th Indust Waste Conf, Eng Bull Purdue Univ, Eng Ext Ser 297-308. Cited In: HSDB, 2002.

McMaster. 1990. Review of neurotox test data for the C9 aromatic hydrocarbons. Memorandum from S. McMaster, Toxic Effects Branch to A. Auletta, Toxics Effects Branch, Office of Toxic Substances, U.S. EPA. Washington, D.C. Cited In: U.S. EPA, 1994a.

MDEQ. 1998. Addendum: 97-033EQ. Air pollution control rules. Part 2. Air use approval. R 336.1224 to R 336.1232 and R 336.1299. Effective date: November 10, 1998. Michigan Department of Environmental Quality (MDEQ), Air Quality Division, Lansing, MI.

MDEQ. 2003. List of screening levels (ITSL, IRSL and SRSL). Verification date: January 22, 2003. Michigan Department of Environmental Quality (MDEQ), Air Quality Division, Lansing, MI.

Mikulski, P.I. and Wiglusz, R. 1975. The comparative metabolism of mesitylene, pseudocumene, and hemimellitene in rats. *Toxicol Appl Pharmacol* **31(1)**:21-31. Cited In: Cavender, 1994.

MOEE. 1996. Three-year Plan for Standards-setting. Standards Development Branch, Ministry of Environment and Energy, Ontario.

MOE. 1999a. Summary of Point of Impingement Standards, Ambient Air Quality Criteria (AAQCs) and Approvals Screening Levels (ASLs). Standards Development Branch, Ontario Ministry of the Environment, Toronto, Ontario.

MOE. 1999b. Setting Environmental Quality Standards in Ontario: The Ministry of the Environment's Standards Plan. Standards Development Branch, Ministry of Environment, Ontario.

MOE. 2005. Summary of O.Reg 419/05 Standards and Point of Impingement Guidelines & Ambient Air Quality Criteria (AAQCs). Standards Development Branch, Ontario Ministry of the Environment. December.

MOE, 2005. Information Draft on the Development of Ontario Air Standards for 1,2,4-Trimethylbenzene. Standards Development Branch, Ontario Ministry of the Environment. July. URL: http://www.ene.gov.on.ca/envision/air/airquality/standards.htm

MOE, 2006. Rationale for the Development of Ontario Air Standards for Trimethylbenzenes. Standards Development Branch. Ontario Ministry of the Environment. June.URL: http://www.ene.gov.on.ca/envision/air/airquality/standards.htm

NPRI. 1995. National Pollutant Release Inventory. Report and on-line Database of 1995. URL:http://www.pwc.bc.doe.ca/ep/npri/index.html

NPRI. 1996. National Pollutant Release Inventory. Report and on-line Database of 1996. URL:http://www.pwc.bc.doe.ca/ep/npri/index.html

NPRI. 1997. National Pollutant Release Inventory. Report and on-line Database of 1997. URL:http://www.pwc.bc.doe.ca/ep/npri/index.html.

NPRI. 1998. National Pollutant Release Inventory. Report and on-line Database of 1998. URL:http://www.pwc.bc.doe.ca/ep/npri/index.html

NPRI. 1999. National Pollutant Release Inventory. Report and on-line Database of 1999. URL:http://www.pwc.bc.doe.ca/ep/npri/index.html

NPRI. 2000. National Pollutant Release Inventory. Report and on-line Database of 2000. URL:http://www.pwc.bc.doe.ca/ep/npri/index.html

NPRI. 2001. National Pollutant Release Inventory. Report and on-line Database of 2001. URL:http://www.pwc.bc.doe.ca/ep/npri/index.html

NPRI. 2002. National Pollutant Release Inventory. Report and on-line Database of 2002. URL:http://www.pwc.bc.doe.ca/ep/npri/index.html

NPRI. 2003. National Pollutant Release Inventory. Report and on-line Database of 2003. URL:http://www.pwc.bc.doe.ca/ep/npri/index.html

NYDEC. 1991. Guidelines for the control of toxic ambient air contaminants. New York State Department of Environmental Conservation (NYDEC), Division of Air Resources, Albany, NY. 20 pp. + Appendices.

NYDEC. 1995. General Process Emission Sources. Chapter III. Air Resources. Part 212. New York State Department of Environmental Conservation (NYDEC), Division of Air Resources.

NYDEC. 2000. DAR-2 AGC/SGC Tables. New York State Department of Environmental Conservation (NYDEC), Division of Air Resources, Bureau of Stationary Sources.

Omori, T. and Yamada, K. 1969. *Agr Biol Chem* **33**: 979-85. Cited In: HSDB, 2002.

Park, J.H. and Lee, H.J. 1993. Estimation of bioconcentration factor in fish, adsorption coefficient for soils and sediments and interfacial tension with water for organic nonelectrolytes based on the linear solvation energy relationships. *Chemosphere* **26(10)**: 1905-1916.

Pate, C.T. *et al.* 1976. *J Environ Sci Health -Environ Sci Eng* **A11**:1-10. Cited In: HSDB, 2002.

Rees. 1989. Section 4 testing of C9 aromatic hydrocarbons: Neurotoxicity data. Memorandum from C. Rees, Toxic Effects Branch to C. Auer, Health and Environmental Review Division, Office of Toxic Substances, U.S. EPA. Washington, D.C. Cited In: U.S. EPA, 1994a.

RTECS (Registry of Toxic Effects of Chemical Substances). 2000. Registry of Toxic Effects of Chemical Substances. Computerized interactive database produced by the National Institute for Occupational Safety and Health (NIOSH). Issue 2000-2. May, 2000.

Saillenfiat, A.M., Gallissot, F., Sabate, J.P. and Morel, G. 2005. Developmental toxicity of two trimethylbenzene isomers, mesitylene and pseudocumene, in rats following inhalation exposure. *Food chem toxicol* **43**:1055-1063.

Sandmeyer, E.E. 1981. Aliphatic Hydrocarbons. *In*: Patty's Industrial Hygiene and Toxicology. 4th Ed. Vol. 2B. G.D. Clayton and F. Clayton, Eds. John Wiley and Sons, Inc., Toronto. 3175-3220. Cited In: Zahlsen *et al*., 1990.

Sax, N.I., and Lewis, R.J. Sr. 1987. Hawley's Condensed Chemical Dictionary. 11th Ed. Van Nostrand Reinhold. New York, NY. Cited In: CalARB, 1997a and U.S. EPA, 1994a.

Seed. 1989. Review of Section 4 study - Three generation reproduction/fertility study in rats with C9 aromatic hydrocarbons. Memorandum from J. Seed, Toxics Effects Branch to N. Chudhari, Test Rules Development Branch, Office of Toxic Substances, U.S. EPA. Washington, D.C. Cited In: U.S. EPA, 1994a.

Sills, R. 2000. Personal Communication. State of Michigan. Michigan Department of Environmental Quality. Air Quality Division. March 3, 2000.

Smith, J.H., and Harper, J.C. 1981. Proceedings 12th Conference on Environmental Toxicology 3,4 and 5th November, 1981. Airforce Aerospace Medical Research Laboratory, Ohio. Cited In: HSDB, 2002.

Swann, R.L., Laskowski, D.A., McCall, P.J., *et al*. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio and water solubility. *Res Rev* **85**: 17-28.

Swiercz, R., Rydzynski, K., Wasowicz, W., Majcherek, W. and Wesolowski, W. 2002. Toxicokinetics and metabolism of pseudocumene (1,2,4-trimethylbenzene) after inhalation exposure in rats. *Int J Occup Med Environ Health* **15(1)**:37-42.

Swiercz, R., Wiaderna, D., Wasowicz, W., and Rydzynski, K. 2003. Pseudocumene in brain, liver, lung and blood of rats after single and repeated inhalation exposure. *Int J Occup Med Environ Health* **16(1)**:61-66.

TRI92. 1994. 1992 Toxic Releases Inventory. Office of Pollution Prevention and Toxics. United States Environmental Protection Agency. Washington, D.C. Cited In: U.S. EPA, 1994a.

TPHCWG. 1997. Development of fraction specific reference doses (RfDs) and reference concentrations (RfCs) for total petroleum hydrocarbons (TPH). Volume IV. TPH Criteria Working Group, Toxicology Technical Action Group.

Tuazon, E.C. *et al.* 1986. *Environ Sci Technol* **20**: 383-87. Cited In: HSDB, 2002.

U.S. EPA. 1987. Health effects assessment for trimethylbenzenes. Office of Research and Development. United States Environmental Protection Agency. Washington, D.C. 12 pp. ECAO-CIN-H059. Cited In: U.S. EPA, 1994a.

U.S. EPA, 1988. Drinking water health advisory for 1,2,4-trimethylbenzene. Office of Research and Development. United States Environmental Protection Agency. Washington, D.C. 14 pp. ECAO-CIN-W029. Cited In: U.S. EPA, 1994a.

U.S. EPA. 1991. RAB Pre-RM1 Presentation for the C9 Aromatic Hydrocarbon Fraction. Risk Assessment Branch (prepared by E. Brandt). Existing Chemicals Division. Office of Toxic Substances. United States Environmental Protection Agency. Washington, D.C. Cited In: U.S. EPA, 1994a.

U.S. EPA. 1994a. Chemical summary for 1,2,4-trimethylbenzene. Office of Pollution Prevention and Toxics. United States Environmental Protection Agency. Washington, D.C.

U.S. EPA. 1994b. Chemicals in the environment: 1,2,4-trimethylbenzene (CAS No. 95-63-6). Office of Pollution Prevention and Toxics. United States Environmental Protection Agency. Washington, D.C.

U.S. EPA. 1994c. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. United States Environment Protection Agency. URL: http://www.epa.gov/iris/backgr-d.htm

U.S. EPA. 1998. TRI On-site and Off-site Reported Releases, Trend Report for 1,2,4-Trimethylbenzene, U.S., 1988-1998, Original Industries. United States Environmental Protection Agency Toxic Release Inventory. Accessed on-line: July 24, 2000. http://www.epa.gov/cgi-bin/broker?...gram=xp_tri.sasmacr.tristart.macro.

Van Der Linden, A.C. 1978. *Dev Biodegrad Hydrocarbons* **1**: 165-200. Cited In: HSDB, 2002.

Verschueren, K. ed. 1983. Handbook of Environmental Data on Organic Chemicals. 2nd Ed. Van Nostrand Reinhold Co. New York. pp. 1162-1163. Cited In: U.S. EPA, 1994a.

Wiaderna, D., Gralewica, S., and Tomas, T. 1998. Behavioural changes following a four-week inhalation exposure to hemimellitene (1,2,3-trimethylbenzene) in rats. *J Occup Med Env Health* **11(4)**:319-334.

Wiaderna, D., Gralewicz, S., and Tomas, T. 2002. Assessment of long-term neurotoxic effects of exposure to mesitylene (1,3,5-trimethylbenzene) based on the analysis of selected behavioural responses. *J Occup Med Env Health* **15(4)**:385-391.

Wiglusz, R., Delag, G. and Mikulski, P. 1975. Serum enzymes activity of mesitylene vapour treated rats. *Bull Inst Marit Trop Med (Gdynia)* **26(3-4)**: 303-313. Cited In: Cavender, 1994.

Zahlsen, K., Nilsen, A.M., Eide, I. and Nilsen, O.G. 1990. Accumulation and distribution of aliphatic (n-nonane), aromatic (1,2,4-trimethylbenzene) and naphthenic (1,2,4-trimethylcyclohexane) hydrocarbons in the rat after repeated inhalation. *Pharm Toxicol* **67**:436-440.

10.0 Appendix: Agency-Specific Reviews of Air Quality Guidelines

10.1 Agency-Specific Summary: Federal Government of Canada

1. Name of Chemical:
   1,2,3-Trimethylbenzene (CAS no. 526-73-8)
   1,2,4-Trimethylbenzene (CAS no. 95-63-6)
   1,3,5-Trimethylbenzene (CAS no. 108-67-8)
   Trimethylbenzene isomers (CAS no. 25551-13-7)

2. Agency: Canadian Environmental Protection Act (CEPA) under the auspices of Health Canada.

3. Guideline Value(s):

   No guideline is listed.

4. Application:

   Under the Canadian Environmental Protection Act (CEPA), the Ministers of the Environment and Health are advised to investigate various substances with the potential to cause adverse effects on the environment and human health. In 1994, 44 chemicals were on the first Priority Substances List (PSL1). In addition to this, in 1995, the second PSL List (PSL2) was established and the 25 substances identified were scheduled to be evaluated over the upcoming years.

   Some of the substances listed in Health Canada (1996) have Tolerable Daily Intake (TDI) values for non-carcinogenic effects, which are expressed on a body weight basis (e.g., mg/kg/day). These values are the total intakes by ingestion, to which it is believed that a person can be exposed over a lifetime without deleterious effects.

5. Documentation Available:

   Health Canada. 1996. Health-based tolerable daily intakes/ concentrations and tumorigenic doses/ concentrations for Priority Substances. Environmental Health Directorate, Health Protection Branch, Health Canada.

Key Reference(s):

No information.

6. Peer Review Process and Public Consultation:

   Not applicable.

7. Status of Guideline:

   Not applicable.

8. Key Risk Assessment Considerations:

   Not applicable.

9. Key Risk Management Considerations:

   Not applicable.

10. Multimedia Considerations of Guidelines:

    Not applicable.

11. Other Relevant Factors:

    No information.

10.2 Agency-Specific Summary: Federal Government of the United States

1. Name of Chemical:
   1,2,3-Trimethylbenzene (CAS no. 526-73-8)
   1,2,4-Trimethylbenzene (CAS no. 95-63-6)
   1,3,5-Trimethylbenzene (CAS no. 108-67-8)
   Trimethylbenzene isomers (CAS no. 25551-13-7)

2. Agency: U.S. Environmental Protection Agency (U.S. EPA)

3. Guideline Value(s):

   No guideline is listed.

4. Application:

   The IRIS database is designed to provide consistent information on chemical substances used in risk assessments, decision-making and regulatory activities. The main intention of IRIS is to provide information which can be used towards the protection of public health through risk assessment and risk management. The values presented in IRIS do not represent guidelines on their own. IRIS also contains a summary of current American government regulatory actions under various mandates.

5. Documentation Available:

   No information.

   Key Reference(s):

   No information.

6. Peer Review Process and Public Consultation:

   No information.

7. Status of Guideline:

   Not applicable.

8. Key Risk Assessment Considerations:

   Not applicable.

9. Key Risk Management Considerations:

   Not applicable.

10. Multimedia Considerations of Guidelines:

    No information.

11. Other Relevant Factors:

    No information.

10.3 Agency-Specific Summary: California

1. Name of Chemical:
   1,2,3-Trimethylbenzene (CAS no. 526-73-8)
   1,2,4-Trimethylbenzene (CAS no. 95-63-6)
   1,3,5-Trimethylbenzene (CAS no. 108-67-8)
   Trimethylbenzene isomers (CAS no. 25551-13-7)

2. Agency: California Environmental Protection Agency (CalEPA)

3. Guideline Value(s):

   No guideline is listed.

4. Application:

   "The intent of the Committee in developing the guideline was to provide risk assessment procedures for use in the Air Toxics 'Hot Spots' program." (CAPCOA, 1993). This program is based on a California State Law, the Air Toxics 'Hot Spots' Information and Assessment Act of 1987 (Health and Safety Code Section 44360 et Seq.). The act specifies how local Air Pollution Control Districts determine which facilities in the area will prepare a health risk assessment, how such health risk assessments should be prepared, and how the results are to be prioritized. These Guidelines were prepared to provide consistent risk assessment methods and report presentation to: 1) compare one facility against another, 2) expedite the review of risk assessments by reviewing agencies, and 3) minimize revisions and re-submission of risk assessments. The various health-based exposure levels developed for and employed in this program should not be used outside the framework of the program. That is to say, the State of California does not consider them to be general, independent, legally enforceable air quality guidelines or limit values at this time.

5. Documentation Available:

   No information.

   Key Reference(s):

   No information.

6. Peer Review Process and Public Consultation:

   No information.

7. Status of Guideline:

   Not applicable.

8. Key Risk Assessment Considerations:

   Not applicable.

9. Key Risk Management Considerations:

   Not applicable.

10. Multimedia Considerations of Guidelines:

    No information.

11. Other Relevant Factors:

    No information.

10.4 Agency-Specific Summary: Massachusetts

1. Name of Chemical:
   1,2,3-Trimethylbenzene (CAS no. 526-73-8)
   1,2,4-Trimethylbenzene (CAS no. 95-63-6)
   1,3,5-Trimethylbenzene (CAS no. 108-67-8)
   Trimethylbenzene isomers (CAS no. 25551-13-7)

2. Agency: Massachusetts Department of Environmental Protection (MDEP)

3. Guideline Value(s):

   No guideline is listed.

4. Application:

   "...The Division of Air Quality Control, which is responsible for implementing the Department's air programs, plans to employ the AALs in the permitting, compliance, and enforcement components of the commonwealth's air program in general, and the air toxics program in particular." (MADEP, 1990, Volume 1, p. ix). The Massachusetts Department of Environmental Protection (MADEP) is responsible for developing, among other environmental programs, the air toxics program, the primary objective of which is to protect human health. The limits generated by the program are "health-based only and were developed without regard to production volume, exposure level, or regulatory implication. Similarly, economic and control technology issues are neither discussed nor considered here." (MADEP, 1990, Volume 1, p. 4). Thus, the ambient air levels developed in this process are not to be considered as legally-enforceable air standards, rather, they should be employed as guidelines in the development of subsequent regulatory action.

5. Documentation Available:

   No information.

   Key Reference(s):

   No information.

6. Peer Review Process and Public Consultation:

   No information.

7. Status of Guideline:

Not applicable.

8. Key Risk Assessment Considerations:

   Not applicable.

9. Key Risk Management Considerations:

   Not applicable.

10. Multimedia Considerations of Guidelines:

    No information.

11. Other Relevant Factors:

    No information.

10.5 Agency-Specific Summary: Michigan

1. Name of Chemical:
   1,2,3-Trimethylbenzene (CAS no. 526-73-8)
   1,2,4-Trimethylbenzene (CAS no. 95-63-6)
   1,3,5-Trimethylbenzene (CAS no. 108-67-8)
   Trimethylbenzene isomers (CAS no. 25551-13-7)

2. Agency: Michigan Department of Environmental Quality

3. Guideline Value(s):

   MDEQ has adopted 1,230 $\mu g/m^3$ for its 8-hour Initial Threshold Screening Level (ITSL) for total trimethylbenzene.

4. Application:

   The screening levels are health-based screening levels for non-carcinogenic effects under Michigan's air toxic rules. These values are only used as a tool for the evaluation of ambient air impacts from new or modified air emission sources when a permit is requested. These values are not considered as general ambient air quality levels nor are they considered standards. The air toxics rules require that each source apply the best available control technology for toxics (T-BACT) and the maximum ambient concentration of each toxic air contaminant cannot exceed its screening level. Some exceptions to the T-BACT requirement include processes emitting low potency carcinogens or non-carcinogens that have relatively low toxicity.

5. Documentation Available:

   MDEQ. 1998. Addendum: 97-033EQ. Air pollution control rules. Part 2. Air use approval. R 336.1224 to R 336.1232 and R 336.1299. Effective date: November 10, 1998. Michigan Department of Environmental Quality (MDEQ), Air Quality Division, Lansing, MI.

   MDEQ. 2003. List of screening levels (ITSL, IRSL and SRSL). Verification date: January 22, 2003. Michigan Department of Environmental Quality (MDEQ), Air Quality Division, Lansing, MI.

   Sills, R. 2000. Personal Communication. State of Michigan. Michigan Department of Environmental Quality. Air Quality Division. Lansing, Michigan. March 3, 2000.

   Key Reference(s):

ACGIH. 2002a. Documentation of the threshold limit values and biological exposure indices. Sixth Edition. American Conference of Governmental Industrial Hygienists (ACGIH) Inc., Cincinnati, OH.

ACGIH. 2002b. Guide to occupational exposure values – 2002. Compiled by the American Conference of Governmental Industrial Hygienists (ACGIH) Inc., Cincinnati, OH.

6. Peer Review Process and Public Consultation:

   No information.

7. Status of Guideline:

   Current. An updated list of screening levels that have been revised or newly established is produces every two months while a complete list of all screening levels is published at the beginning of each year.

8. Key Risk Assessment Considerations:

   The ITSL for TMB of 1,230 $\mu g/m^3$ is based on the ACGIH TLV-TWA of 123 mg/m^3 for mixed trimethylbenzene isomers. The ACGIH TLV-TWA is converted to the ITSL by dividing by a factor of 10 for the protection of sensitive subpopulations and another factor of 10 for adjustment of the intermittent nature of occupational exposure to a continuous lifetime exposure (Sills, 2000).

9. Key Risk Management Considerations:

   These considerations are performed separately by the permitting section. No other specific information is available for this chemical assessment.

10. Multimedia Considerations of Guidelines:

    No information.

11. Other Relevant Factors:

    No information.

10.6 Agency-Specific Summary: North Carolina

1. Name of Chemical:
   1,2,3-Trimethylbenzene (CAS no. 526-73-8)
   1,2,4-Trimethylbenzene (CAS no. 95-63-6)
   1,3,5-Trimethylbenzene (CAS no. 108-67-8)
   Trimethylbenzene isomers (CAS no. 25551-13-7)

2. Agency: Department of Environment and Natural Resources (DENR)

3. Guideline Value(s):

   No guideline listed.

4. Application:

   This acceptable ambient air level is a product of initial recommendations by the Scientific Advisory Board (SAB) from which averaging times are assigned by the staff of the Toxics Protection Branch. These toxic air pollutant values are considered guidelines only and apply to all facilities that emit a toxic air pollutant that are required to have a permit under 15A NCAC 2Q.0700 of North Carolina Air Quality Rules. A facility shall not emit any toxic air pollutant under North Carolina Air Quality Rules in such quantities that may cause or contribute beyond the premises (adjacent property boundary) to any significant ambient air concentration that may adversely affect human health.

5. Documentation Available:

   No information.

   Key Reference(s):

   None.

6. Peer Review Process and Public Consultation:

   Not applicable.

7. Status of Guideline:

   Not applicable.

8. Key Risk Assessment Considerations:

Not applicable.

9. Key Risk Management Considerations:

   Not applicable.

10. Multimedia Considerations of Guidelines:

    Not applicable.

11. Other Relevant Factors:

    No information.

10.7 Agency-Specific Summary: World Health Organization

1. Name of Chemical:
   1,2,3-Trimethylbenzene (CAS no. 526-73-8)
   1,2,4-Trimethylbenzene (CAS no. 95-63-6)
   1,3,5-Trimethylbenzene (CAS no. 108-67-8)
   Trimethylbenzene isomers (CAS no. 25551-13-7)

2. Agency:

   World Health Organization - Protection of the Human Environment (WHO-PHE);
   World Health Organization - Europe (WHO-Europe)

3. Guideline Value(s):

   No guideline is listed.

4. Application:

   The WHO Air Quality Guidelines are designed to reduce air pollution and to protect human health. ... “The Guidelines are intended to provide background information and guidance to national or international authorities in making risk assessment and risk management decisions. In providing pollutant levels below which exposure, for lifetime or for a given period of time, does not constitute a significant public health risk, the guidelines form a basis for setting (inter)national standards or limit values for air pollutants.”

5. Documentation Available:

   No information.

   Key Reference(s):

   No information.

6. Peer Review Process and Public Consultation:

   Not applicable.

7. Status of Guideline:

   Not applicable.

8. Key Risk Assessment Considerations:

Not applicable.

9. Key Risk Management Considerations:

   Not applicable.

10. Multimedia Considerations of Guidelines:

    Not applicable.

11. Other Relevant Factors:

    No information.

11.0 Acronyms, Abbreviation, and Definitions

AAL *Allowable Ambient Level* (Massachusetts) or *Acceptable Ambient Level* (North Carolina)

AAQC *Ambient Air Quality Criteria* - used by the Ontario Ministry of the Environment to define the potential for causing an adverse effect

ACGIH *American Conference of Governmental Industrial Hygienists* - a non-governmental organization which establishes occupational safety exposure limits for workers

AGC *Annual Guideline Concentration* (New York State)

CAPCOA *California Air Pollution Control Officers Association*

CAS *Chemical Abstracts Service* - ascribes a unique, identification (registry) number to each chemical to help clarify multiple listings for the same chemical structure

CCME *Canadian Council of Ministers of the Environment*

CEPA *Canadian Environmental Protection Act*

CEQ *Commission on Environmental Quality* - Department in state agency of Texas

DEC *Department of Environmental Conservation* - Department in state agency of New York

DENR *Department of Environment and Natural Resources* - Department in state agency of North Carolina

DEP *Department of Environmental Protection* - Department in state agencies of Massachusetts

DEQ *Department of Environmental Quality* - Department in state agencies of Michigan

ESL *Effects Screening Level* (Texas)

GLC *Ground Level Concentration* - the concentration of contaminant predicted by dispersion modelling

IARC *International Agency for Research on Cancer*

IRIS *Integrated Risk Information System* - a database published by the U.S. EPA containing risk assessment information on a wide range of chemicals

IRSL *Initial Risk Screening Level* - a limit corresponding to a one in a million lifetime risk of cancer used by Michigan for screening new sources of emissions

ITSL *Interim Threshold Screening Level* - similar to the IRSL, however, derived for the RfC for non-carcinogens

LC_{50} *Median Lethal Concentration* - the concentration of a substance in the medium (*e.g.*, air, water, soil) to which a test species is exposed, that will kill 50% of the population of that given species

LOAEL *Lowest-Observed-Adverse-Effect Level*

LOEC *Lowest-Observed-Effect Concentration*

MOEE *Ontario Ministry of the Environment and Energy* - as known between 1993 and 1997, which is now known as OMOE or Ontario Ministry of the Environment

NIOSH *National Institute for Occupational Safety and Health* (an agency of the U.S. Department of Health and Human Services)

NPRI *National Pollutant Release Inventory*

OEHHA *Office of Environmental Health Hazard Assessment* (California EPA)

POI *Point of Impingement* - used in conjunction with dispersion modelling to define the area in which the maximum ground level concentration (GLC) of a contaminant is predicted to occur

PSL1 *First Priority Substances List* (CCME)

PSL2 *Second Priority Substances List* (CCME)

RD_{50} *Median Respiration Rate Decrease* - the dose at which respiration rate is decreased 50%

RfC *Reference Concentration* - an estimate of a daily inhalation exposure not likely to induce adverse health effects during a lifetime

RfD	*Reference Dose* - an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious non-cancer effects during a lifetime
RTECS	*Registry of Toxic Effects of Chemical Substances* - database maintained by NIOSH
SGC	*Short-term Guideline Concentration* (New York State)
SRSL	*Secondary Risk Screening Level* - a limit corresponding to one in one-hundred-thousand lifetime risk of cancer used by Michigan for screening new sources of emissions
TDI	*Tolerable Daily Intake* (Health Canada) – the total intake by ingestion that a person can be exposed over a lifetime without deleterious effects
TLV	*Threshold Limit Value* - an exposure concentration that should not induce an adverse effect in a work environment
TWA	*Time-Weighted-Average* - allowable exposure averaged over an 8-hour workday or 40-hour work week
U.S. EPA	*United States Environmental Protection Agency*
WHO	*World Health Organization*
ppm	parts per million
mg	a milligram, one thousandth of a gram
µg	a microgram, one millionth of a gram