Development Support Document
Final, October 15, 2007
Accessible 2013
Revised Odor Value, September 14, 2015

Methyl n-Amyl Ketone

CAS Registry Number: 110-43-0

Prepared by

Angela Curry, M.S.

Toxicology Section

Chief Engineer's Office
TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Revision History

Original Development Support Document (DSD) posted as final on October 15, 2007.

Revised DSD September 14, 2015: the odor-based value was withdrawn because methyl n-amyl ketone does not have a pungent, disagreeable odor (TCEQ 2015).

TABLE OF CONTENTS

TABLE OF CONTENTS ..... **II**

LIST OF TABLES ..... **III**

CHAPTER 1 SUMMARY TABLES **1**

CHAPTER 2 MAJOR SOURCES OR USES **3**

CHAPTER 3 ACUTE EVALUATION **3**

3.1 HEALTH-BASED ACUTE REV AND ^{ACUTE}ESL 3
3.1.1 Physical/Chemical Properties and Key Studies *3*
3.1.1.1 Physical/Chemical Properties 3
3.1.1.2 Essential Data and Key Studies 3
3.1.1.2.1 Human Studies 3
3.1.1.2.2 Animal Studies 3
3.1.2 Mode-of-Action (MOA) Analysis *4*
3.1.3 Dose Metric *5*
3.1.4 Point of Departure for the Key and Supporting Studies *5*
3.1.5 Dosimetric Adjustments *5*
3.1.5.1 Default Exposure Duration Adjustments 5
3.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure 5
3.1.6 Adjustments of the POD_{HEC} and Critical Effect *6*
3.1.6.1 Critical Effect 6
3.1.6.2 Uncertainty Factors (UFs) 6
3.1.7 Health-Based Acute ReV and ^{acute}ESL *7*
3.2. WELFARE-BASED ACUTE ESLS 7
3.2.1 Odor Perception *7*
3.2.2 Vegetation Effects *8*
3.3 SHORT-TERM ESL 8

CHAPTER 4 CHRONIC EVALUATION **8**

4.1 NONCARCINOGENIC POTENTIAL 8
4.1.1 Physical/Chemical Properties and Key Studies *8*
4.1.2 MOA Analysis *9*
4.1.3 PODs for Key Study and Supporting Studies *9*
4.1.4 Dosimetric Adjustments *9*
4.1.4.1 Default Exposure Duration Adjustments 9
4.1.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure 10
4.1.5 Adjustments of the POD_{HEC} and Critical Study *10*
4.1.5.1 Uncertainty Factors 10
4.1.5.1.1 Monkey Study 10
4.1.5.1.2 Rat Study 11
4.1.5.2 Critical Study 11
4.1.6 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ *11*
4.2. CARCINOGENIC POTENTIAL 12
4.3. WELFARE-BASED CHRONIC ESL 12
4.4 LONG-TERM ESL 12

CHAPTER 5 REFERENCES 13

5.1 REFERENCES CITED IN THE DEVELOPMENT SUPPORT DOCUMENT 13
5.2 OTHER STUDIES AND DOCUMENTS REVIEWED BY THE TS 14

LIST OF TABLES

TABLE 1 HEALTH- AND WELFARE-BASED VALUES 1
TABLE 2 CHEMICAL AND PHYSICAL DATA 2
TABLE 3 DERIVATION OF THE ACUTE REV AND ^{ACUTE}ESL USING HUMAN DATA 7
TABLE 4 ODOR STUDIES CONDUCTED FOR MAK 8
TABLE 5 DERIVATION OF THE CHRONIC REV AND ^{CHRONIC}ESL 12

Chapter 1 Summary Tables

Table 1 provides a summary of health- and welfare-based values based on an acute and chronic evaluation of methyl n-amyl ketone (MAK). Table 2 provides summary information on MAK's physical/chemical data.

Table 1 Health- and Welfare-Based Values

Short-Term Values	**Concentration**	**Notes**
^{acute}ESL [1 h] (HQ = 0.3)	4500 µg/m^3 (960 ppb) **Short-Term ESL for Air Permit Reviews**	**Critical Effect**: Eye irritation in humans
acute ReV (HQ = 1.0)	15000 µg/m^3 (3200 ppb) *	**Critical Effect**: Same as Above
^{acute}ESL$_{odor}$	---	Fruity odor
^{acute}ESL$_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
^{chronic}ESL$_{nonlinear(nc)}$ (HQ = 0.3)	840 µg/m^3 (180 ppb) **Long-Term ESL for Air Permit Reviews**	**Critical Effect**: Freestanding NOAEL, no adverse effects observed in rats and monkeys
chronic ReV (HQ = 1.0)	2800 µg/m^3 (610 ppb) *	**Critical Effect**: Same as Above
^{chronic}ESL$_{linear(c)}$ ^{chronic}ESL$_{nonlinear(c)}$	---	No data found
^{chronic}ESL$_{veg}$	---	No data found

* Values that may be used for review of ambient air data

Abbreviations used: **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Levels; **ReV**, Reference Value; **^{acute}ESL**, acute health-based ESL; **^{acute}ESL$_{odor}$**, acute odor-based ESL; **^{acute}ESL$_{veg}$**, acute vegetation-based ESL; **^{chronic}ESL$_{nonlinear(nc)}$**, chronic health-based ESL for nonlinear dose-response noncancer effects; **^{chronic}ESL $_{linear(c)}$**, chronic health-based ESL for linear dose-response cancer effect; **^{chronic}ESL $_{nonlinear(c)}$**, chronic health-based ESL for nonlinear dose-response cancer effect; and **^{chronic}ESL$_{veg}$**, chronic vegetation-based ESL

Table 2 Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	$C_7H_{14}O$	Chemfinder 2004
Chemical Structure		Chemfinder 2004
Molecular Weight	114.19	Chemfinder 2004
Physical State	Liquid	Chemfinder 2004
Color	Colorless to white	Chemfinder 2004
Odor	Fruity	ACGIH 2001
CAS Registry Number	110-43-0	Chemfinder 2004
Synonyms	2-heptanone; Butyl Acetone; Heptan-2-one; Ketone C-7; MAK; Methyl n-amyl ketone; methyl (n-amyl) ketone (2-heptanone); Methyl Pentyl Ketone; methyl amyl ketone; n-amyl methyl ketone; amyl methyl ketone; amylmethylketone [2-heptanone]	Chemfinder 2004
Solubility in water	0.43% (by wt)	HSDB 2006
Log Kow or Pow	1.98	HSDB 2006
Vapor Pressure	1.6 mm Hg at 25 ^{0}C	HSDB 2006
Vapor Density (air = 1)	3.9	HSDB 2006
Density (water = 1)	0.8324 at 0 ^{0}C/4 ^{0}C; 0.8197 at 15 ^{0}C/4 ^{0}C; 0.8068 at 30 ^{0}C/4 ^{0}C	HSDB 2006
Melting Point	-31 ^{0}C	Chemfinder 2004
Boiling Point	150 ^{0}C	Chemfinder 2004
Conversion Factors	1μg/m^3 =0.214ppb 1 ppb= 4.67 μg/m^3	Toxicology Section

Chapter 2 Major Sources or Uses

Methyl n-amyl ketone (MAK) occurs naturally in clove and cinnamon bark oil and is also produced commercially. MAK is used as a solvent in metal roll coatings, in synthetic resin finishes and lacquers, as a flavoring agent, and in perfumes (ACGIH 2001).

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ^{acute}ESL

3.1.1 Physical/Chemical Properties and Key Studies

3.1.1.1 Physical/Chemical Properties

MAK is a liquid and is highly water soluble with a moderate vapor pressure. It has a marked fruity odor (refer to Section 3.2.1). The chemical and physical properties of MAK are summarized in Table 2.

3.1.1.2 Essential Data and Key Studies

At lower concentrations, odor perception and irritation of the mucous membranes in the upper respiratory tract and eyes have been reported from investigations in humans. Neurological effects in animals have been reported to occur at increasing concentrations.

3.1.1.2.1 Human Studies

Cometto-Muniz *et al*. (1999) used 1-butanol and MAK as stimuli to measure detectability functions for odor, nasal pungency, and eye irritation of the two substances alone and in binary mixtures. Nasal pungency responses were tested in subjects lacking olfaction (anosmics), and eye irritation responses were tested in subjects with olfaction (normosmics) and anosmics. Detectability functions for the odor of MAK were found to lie at concentrations of about three orders of magnitude lower than the corresponding functions for nasal pungency. The ocular mucosa seemed more sensitive than the nasal mucosa; therefore, eye irritation was the endpoint used to develop the acute ReV. Stimuli were delivered as vapors from cylindrical, squeezable bottles. For ocular testing, the bottles had a cap of the sort used in variable-volume dispensers, leading to a 35ml, roughly conical, reservoir, the rim of which was placed around the eye, allowing separate testing of each eye upon squeezing of the bottle (Cometto-Muniz 1991). Air concentrations were verified by gas chromatography. The level at which human volunteers did not report eye irritation was 32 parts per million (ppm). This value was determined from visual inspection of a figure provided in the study based on 128 trials by eight subjects (Figure 4, Cometto-Muniz *et al*. 1999).

3.1.1.2.2 Animal Studies

In a neurobehavioral study conducted by Anger (1979), twelve rats (male, *Sprague-Dawley*)

were divided into two groups of six and tested daily using fixed-interval (FI) and multiple fixed ratio (FR) response tests. Daily test sessions lasted for 1 h. The ratios were 20, 35, or 50 responses per reinforcement. The first group was exposed to MAK by intraperitoneal (ip) injection at dose levels of 18, 37, 74, and 175 milligram per kilogram (mg/kg) 15 minutes (min) before each test session to develop dose-effect information. The second group was exposed to MAK by inhalation at dose levels of 115-1890 ppm for 6-8 h (to simulate the route of industrial exposure), followed by a series of ip injections at dose levels of 37 and 74 mg/kg 15 min before each test, to replicate the findings in the first group. To develop time-course information, 175 mg/kg MAK was injected with varying times elapsing between administration and the test session. Time course data indicated that the behavioral changes seen at 15 min after 175 mg/kg injections persisted for at least 1 h but had vanished by 2.25 h after the injections. Inhalation exposures below 1500 ppm did not cause behavioral changes. Over the course of the study, there was a consistent reduction in the magnitude of the behavioral changes, suggesting that tolerance developed.

In a reproductive/developmental toxicity study conducted by Eastman (1996), 12 rats (male and female Sprague-Dawley) per exposure level were exposed by inhalation to 0, 80, 400, and 1000 ppm MAK 6 h/day, 7 days/week for a total of 34-47 exposures for females (through day 19 of gestation) and 50 exposures for males. The study consisted of 4 phases: pre-mating (14 days), mating (1-14 days), gestation (21-24 days), and early lactation (4 days). No mortalities or exposure-related gross or microscopic lesions were noted in adults. High-dose exposure animals exhibited a decrease in activity and reduction in feed intake. Reduction of activity was also noted to a lesser degree in the mid-dose group. Mid-dose females exhibited a decrease in body weight for the day 0-7 interval. No other effects were noted. There were no mortalities, and no developmental abnormalities in the offspring. The free-standing NOAEL was determined to be 1000 ppm.

In another study (Eastman 1964), three rats per exposure level were exposed to MAK as a vapor in whole-body chambers for 4 h at 5126 ppm, and 6 h at 832, 1437, 2016, and 4169 ppm. Animals were monitored for clinical observations and weight change for 14 days. A LC_{50} of 2000-4000 ppm (6 h) was noted. At 5126 ppm, three animals died shortly after their 4-h exposure. At 4169 ppm, one died after 4 h and the other two died shortly after their 6-h exposure ended. No deaths were noted at 2016 ppm or lower.

3.1.2 Mode-of-Action (MOA) Analysis

Irritation of the mucous membranes in the upper respiratory tract and eyes has been reported from studies conducted in humans. Trigeminal nerve endings are distributed throughout the nasal cavity and appear to function, in part, as a detection system for irritants and potentially noxious chemicals. Trigeminal nerve fibers respond to a variety of substances and are part of what has been traditionally called the common chemical sense (Hessamedin 2000). Results suggest that the mechanism by which an irritant stimulates nasal trigeminal nerve endings involves the binding of the irritant with a specific receptor. The MOA for neurological effects is not known.

3.1.3 Dose Metric

For eye irritation in humans, the dose metric is exposure concentration of the parent chemical. For neurological effects in rats, the MOA of the toxic response is not fully understood and data on other more specific dose metrics is not available (e.g. blood concentration of parent chemical, area under blood concentration curve of parent chemical, or putative metabolite concentrations in blood or target tissue), so exposure concentration of the parent chemical will be used as the default dose metric.

3.1.4 Point of Departure for the Key and Supporting Studies

There were two key studies selected. (1) eye irritation in humans (Cometto-Muniz *et al*. 1999) with a POD equal to the NOAEL of 32 ppm and (2) neurological effects in rats (Anger 1979) with a POD_{animal} equal to the NOAEL of 1500 ppm. Other acute health effects occur at much higher concentrations.

3.1.5 Dosimetric Adjustments

3.1.5.1 Default Exposure Duration Adjustments

When humans were exposed to MAK, the exposure durations were less than 1 min. Mild sensory irritation is a concentration-dependent effect, so the concentration at the 1-h exposure duration was assumed to be equal to the concentration at the 1 min exposure duration. Since the MOA for neurological effects in not known, it is unknown whether both concentration and duration play a role in neurotoxicity. The exposure concentration at the 1-h exposure duration was also conservatively assumed to be equal to the exposure concentration for a 6-h exposure duration.

3.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

Neurotoxicity, the health effect of concern, is a remote effect, so the default dosimetry adjustments from animal-to-human exposure is conducted as a Category 3 vapor. For Category 3 vapors, the default dosimetric adjustment from animal-to-human exposure is:

$$POD_{HEC} = POD_{ADJ} \times [(H_{b/g})_A / (H_{b/g})_H]$$

For MAK, the blood:gas partition coefficients ($H_{b/g}$) for rats or humans is not known so a default value of 1 is used for the regional gas dose ratio (RGDR) (USEPA 1994).

Neurological effects in rats

$$POD_{HEC} = POD_{ADJ} \times RGDR$$
$$POD_{HEC} = 1500 \text{ ppm} \times 1$$
$$POD_{HEC} = 1500 \text{ ppm}$$

3.1.6 Adjustments of the POD_{HEC} and Critical Effect

3.1.6.1 Critical Effect

The critical health effect is eye irritation in humans exposed to MAK because it is the endpoint that occurs at the lowest POD_{HEC} (Cometto-Muniz *et al*. 1999).

3.1.6.2 Uncertainty Factors (UFs)

Both eye irritation in humans and neurological effects in rats are noncarcinogenic effects. The default is to determine a POD and apply UFs to derive a ReV (i.e., assume a nonlinear MOA). The following UFs were applied to the POD_{HEC} of 32 ppm for eye irritation in humans: 10 for intraspecies variability (UF_H), 1 for extrapolation from animals to humans (UF_A), 1 for extrapolation from a LOAEL-to-NOAEL (UF_L), and 1 for database uncertainly (UF_D), the total UF = 10. A full UF_H of 10 was used to account for intraspecies variability. A UF_A of 1 was used because this was a human study. A UF_L of 1 was used because a NOAEL was used as the POD. A database UF_D of 1 was used because the overall acute toxicological database for MAK is high. Both the quality of the studies and the confidence in the acute database is high.

Eye irritation in Humans (Cometto-Muniz et al. 1999)

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D)$$
$$= 32 \text{ ppm} / (10 \times 1 \times 1 \times 1)$$
$$= 32 \text{ ppm} / 10$$
$$= 3.2 \text{ ppm}$$

The following UFs were applied to the POD_{HEC} of 1500 ppm for neurological effects in rats: 10 for intraspecies variability (UF_H), 3 for extrapolation from animals to humans (UF_A), 1 for extrapolation from a LOAEL-to-NOAEL (UF_L), and 1 for database uncertainly (UF_D), the total UF = 30. A full UF_H of 10 was used to account for intraspecies variability. A UF_A of 3 was used for extrapolation from animals to humans because default dosimetric adjustments from animal-to-human exposure were conducted, which accounts for toxicokinetic differences but not toxicodynamic differences. A UF_L of 1 was used because a NOAEL was used as the POD. A database UF_D of 1 was used because the overall acute toxicological database for MAK is extensive. Both the quality of the studies and the confidence in the acute database is high.

Neurological effects in rats (Anger 1979)

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D)$$
$$= 1500 \text{ ppm} / (10 \times 3 \times 1 \times 1)$$
$$= 1500 \text{ ppm} / 30$$
$$= 50 \text{ ppm}$$

3.1.7 Health-Based Acute ReV and ^{acute}ESL

The acute ReV value was rounded to the least number of significant figures for a measured value at the end of all calculations. Rounding to two significant figures, the 1-h acute ReV is 3.2 ppm (15 mg/m^3) or 3200 ppb (15000 µg/m^3) based on Cometto-Muniz *et al*. 1999. The rounded acute ReV was then used to calculate the health-based acute ESL. At the target hazard quotient of 0.3, the acute ESL is 960 ppb (4500 µg/m^3) (Table 4).

Table 3 Derivation of the Acute ReV and ^{acute}ESL Using Human Data

Parameter	**Summary**
Study population	Humans: 4 normosmics; 4 anosmics (Cometto-Muniz *et al*. 1999)
Study quality	High
Exposure Methods	A series of two-fold dilutions of 100% volume chemical
POD_{HEC}	32 ppm (level at which human volunteers did not note eye irritation)
Critical Effects	Eye irritation
Exposure Duration	< 1 min
Extrapolation to 1 h	No adjustment made since mild sensory irritation is concentration dependent
Extrapolated 1 h concentration	32 ppm
Total UFs	10
Interspecies UF	1
Intraspecies UF	10
LOAEL UF	1
Incomplete Database UF	1
Database Quality	High
acute ReV [1 h] (HQ = 1)	**15000 µg/m^3 (3200 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**4500 µg/m^3 (960 ppb)**

3.2. Welfare-Based acute ESLs

3.2.1 Odor Perception

MAK has a marked fruity odor. Published odor threshold values that met the criteria accepted by AIHA and USEPA (AIHA, 1989; USEPA, 1992) are noted in Table 4. Since MAK does not have an odor that is pungent or disagreeable, an $^{acute}ESL_{odor}$ was not developed (TCEQ 2015).

Table 4 Odor Studies Conducted for MAK

Investigator	Odor Detection Threshold Value µg/m3 (ppb)	Comment
Cometto-Muniz & Cain (1993); Cometto-Muniz (1993)	3300 µg/m^3 (710 ppb)	100% detection threshold approved study *
Cometto-Muniz *et al.* (1999)	290 µg/m^3- 650 µg/m^3 (62 ppb – 139 ppb)	approved study *
Nagata (2003)	32 µg/m^3 (6.8 ppb)	approved study *

* Published odor threshold values that met the criteria accepted by AIHA; USEPA and TCEQ (AIHA 1989; USEPA 1992)

3.2.2 Vegetation Effects

No acute vegetative studies were identified for MAK; therefore, an $^{acute}ESL_{veg}$ was not developed.

3.3 Short-Term ESL

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

$^{acute}ESL$ = 4500 µg/m^3 (960 ppb)
acute ReV = 15000 µg/m^3 (3200 ppb)

The health-based $^{acute}ESL$ of 4500 µg/m^3 (960 ppb) is the short-term ESL used for air permit reviews (Table 1).

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties and Key Studies

Refer to Section 3.1.1.1 for a discussion of physical/chemical properties. There were no chronic human studies available for MAK, so only animal studies will be discussed. Because previous studies showed that Methyl butyl ketone possessed neurotoxic properties, investigations were initiated to examine the possible neurotoxic effects of MAK. The selected key studies (Johnson *et al.* 1979 and Lynch *et al.* 1981) published separate results that complement and support each other.

Johnson *et al.* (1979) reported the neurophysical portion of the study, exposing 10 male *Sprague-Dawley* rats and 8 male *Macaca fascicularis* monkeys per exposure group to 0, 131 or 1025 ppm MAK vapors for 6 h/day, 5 days/week for 9 months. No animals showed any clinical signs of

illness during the study. No impairment in grip, or locomotion was observed, and no tissue damage related to MAK exposure was observed in either species.

Lynch *et al.* (1981) reported the results on multiple endpoints including cardiopulmonary function, clinical chemistry, metabolism, and tissue distribution of MAK by exposing 50 male Sprague-Dawley rats and 8 male Macaca fascicularis monkeys per exposure group to 0, 131 or 1025 ppm MAK vapors for 6 h/day, 5 days/week for 10 months. Clinical analysis were conducted on primates after 1, 3, and 6 months of exposure and at study termination. Blood and urine were collected from both species at termination for metabolite identification. Both species were evaluated at monthly intervals for neurological function. Additionally, primates underwent electroencephalograms (EEG), electrocardiograms (EKG), and cardiopulmonary testing. None of these tests demonstrated evidence of neurotoxicity after 6 months of exposure, nor were any effects noted on cardiopulmonary function tests. As reported by Johnson et al. (1979), both species tolerated the exposures without developing any obvious signs of toxicity, or alterations in weight gain. Neither species displayed any gross or microscopic changes in any reproductive organ or tissue examined. The free-standing NOAEL from both key studies was determined to be 1025 ppm for both species.

4.1.2 MOA Analysis

Although MAK has been shown to produce neurotoxic effects after acute exposures to high concentrations, in the studies conducted by Johnson *et al.* (1979) and Lynch *et al.* (1981), toxic endpoints were not observed in rats or monkeys; therefore, a MOA analysis is not possible. Exposure concentration of the parent chemical will be used as the default dose metric since the MOA of the toxic response is not fully understood and data on other more specific dose metrics is not available.

4.1.3 PODs for Key Study and Supporting Studies

In the key studies (Johnson *et al.*, 1979 and Lynch *et al.* 1981), no effects were observed in rats or monkeys. The POD_{animal} is equal to the free-standing NOAEL of 1025 ppm.

4.1.4 Dosimetric Adjustments

4.1.4.1 Default Exposure Duration Adjustments

The animals used in this study were exposed to either 131 or 1025 ppm MAK vapors for 6 h/day, 5 days/wk. It was necessary to adjust the study POD from a discontinuous animal exposure scenario to a continuous exposure scenario POD_{ADJ} as outlined in section 4.2.2 of the guidelines (TCEQ 2006) by using the following equation:

$$POD_{ADJ} = POD \times (D/24\ h) \times (F/days)$$

where: D = Exposure duration, h per day

F = Exposure frequency, days per week

POD_{ADJ} = 1025 ppm x (6/24 h) x (5/7 days)
POD_{ADJ} = 183.04 ppm

4.1.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

Neurotoxicity, the health effect of concern, is a remote effect so the default dosimetry adjustments from animal-to-human exposure is conducted as a Category 3 vapor. For Category 3 vapors, the default dosimetric adjustment from animal-to-human exposure is:

$POD_{HEC} = POD_{ADJ} \times [(H_{b/g})_A / (H_{b/g})_H]$
where: $H_{b/g}$ = ratio of the blood:gas partition coefficient
A = animal
H = human

For MAK, the blood:gas partition coefficient for rats or humans is not known so a default value of 1 is used for the regional gas dose ratio (RGDR) (USEPA 1994).

POD_{HEC} = 183.04 ppm x RGDR
POD_{HEC} = 183.04 ppm x 1
POD_{HEC} = 183.04 ppm

4.1.5 Adjustments of the POD_{HEC} and Critical Study

In the studies conducted by Johnson *et al.* (1979) and Lynch *et al.* (1981), toxic endpoints were not observed in rats and monkeys. A POD_{HEC} based on a free-standing NOAEL was used as the POD and UFs were applied to derive a ReV (i.e., assume a nonlinear MOA for a noncarcinogenic endpoint).

4.1.5.1 Uncertainty Factors

4.1.5.1.1 Monkey Study

The following uncertainty factors (UFs) were applied to the POD_{HEC} of 183.04 ppm for the monkey study: 10 for intraspecies variability (UF_H), 1 for extrapolation from animals to humans (UF_A), 10 to extrapolate from sub-chronic to chronic exposure (UF_{Sub}), and 3 for database uncertainly (UF_D), for a total UF of 300. For the monkey study, an UF_A of 1 was used for extrapolation from animals to humans because monkeys are an animal species that are closer to humans than rodents. The life span of the *Macaca fascicularis* monkey is 31 years; therefore a 10 month study would be considered a sub-chronic study, thus an UF_{Sub} of 10 was used to account for the exposure duration.

A UF_H of 10 was used to account for human variability and a database UF_D of 3 was used because the studies conducted by Johnson *et al.* (1979) and Lynch *et al.* (1981) evaluated a range

of effects in two different species but a dose-response was not observed. In addition, there is an absence of a two generational reproductive/developmental study.

$$\text{chronic ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_{Sub} \times UF_D)$$
$$= 183.04 \text{ ppm} / (10 \times 1 \times 10 \times 3)$$
$$= 183.04 \text{ ppm} / 300$$
$$= 0.61 \text{ ppm} = 610.13 \text{ ppb}$$

4.1.5.1.2 Rat Study

The following uncertainty factors (UFs) were applied to the POD_{HEC} of 183.04 ppm for the rat study: 10 for UF_H, 3 for UF_A, 1 for UF_{Sub}, and 3 for UF_D, for a total UF of 100. For the rat study, an UF_A of 3 was used because default dosimetric adjustments from animal-to-human exposure were conducted, which account for toxicokinetic differences but not toxicodynamic differences. The life span of a *Sprague-Dawley* rat is 2 years; therefore a 10 month study would be considered to be a chronic study, thus an UF_{Sub} of 1 was used to account for the exposure duration.

A UF_H of 10 was used to account for human variability and a database UF_D of 3 was used because the studies conducted by Johnson *et al.* (1979) and Lynch *et al.* (1981) evaluated a range of effects in two different species but a dose-response was not observed. In addition, there is an absence of a two generational reproductive/developmental study.

$$\text{chronic ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_{Sub} \times UF_D)$$
$$= 183.04 \text{ ppm} / (10 \times 3 \times 1 \times 3)$$
$$= 183.04 \text{ ppm} / 100$$
$$= 1.8304 \text{ ppm} = 1830 \text{ ppb}$$

4.1.5.2 Critical Study

The quality of the Johnson *et al.* (1979) and Lynch *et al.* (1981) studies are high. The overall toxicological database for MAK is moderate. A chronic ReV of 610.13 ppb based on the monkey study is the critical study because it is lower than the chronic ReV of 1830 ppb based on the rat study.

4.1.6 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

The chronic ReV value was rounded to the least number of significant figures for a measured value at the end of all calculations. Rounding to two significant figures, the chronic ReV is 610 ppb (2800 µg/m^3). The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{nonlinear(nc)}$. At the target hazard quotient of 0.3, the $^{chronic}ESL_{nonlinear(nc)}$ is 180 ppb (840 µg/m^3) (Table 6).

Table 5 Derivation of the Chronic ReV and ^{chronic}ESL

Parameter	Summary
Study	Sub-chronic repeated dose conducted by Johnson *et al.* (1979) and Lynch *et al.* (1981)
Study Population	50 Rats (*Sprague-Dawley*) 8 Monkeys (*Macaca fascicularis*)
Study Quality	High
Exposure Method	Whole-body chamber
Critical Effects	No adverse effects observed
POD (original animal study)	1025 ppm (free-standing NOAEL)
Exposure Duration	Exposed to either 131 or 1025 ppm MAK vapors for 6/h/day, 5 days/wk for 10 months
Extrapolation to continuous exposure (POD_{ADJ})	183.04 ppm
POD_{HEC} Dosimetry adjustment from animal concentration to HEC	183.04 ppm (RGDR = 1 using default assumption)
Total UFs	300
Interspecies UF	1
Intraspecies UF	10
LOAEL UF	NA
Subchronic to chronic UF	10
Incomplete Database UF	3
Database Quality	Medium
chronic ReV (HQ = 1)	**2800 µg/m^3 (610 ppb)**
^{chronic}ESL$_{nonlinear(nc)}$ (HQ = 0.3)	**840 µg/m^3 (180 ppb)**

4.2. Carcinogenic Potential

No studies were identified for MAK.

4.3. Welfare-Based Chronic ESL

No data were found regarding long-term vegetative effects.

4.4 Long-Term ESL

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

- Chronic ReV = 2800 µg/m^3 (610 ppb)
- $^{chronic}ESL_{nonlinear(nc)}$ = 840 µg/m^3 (180 ppb)

The $^{chronic}ESL_{nonlinear(nc)}$ of 840 µg/m^3 (180 ppb) is the long-term ESL used for air permit reviews (Table 1).

The health-based long-term ESL is much higher than the short-term odor-based ESL of 32 µg/m^3 (6.8 ppb) (Table 1). Thus, if the 1-h modeling concentrations meet the short-term ESL, no acute and chronic adverse effects are expected to occur as a result of exposure to MAK emissions from a permit application facility.

Chapter 5 References

5.1 References Cited in the Development Support Document

American Conference of Governmental Industrial Hygienists (ACGIH). 2001. MAK: TLV® (2001). Chemical Substances 7th Edition Documentation ACGIH® Publication.

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

Anger, WK, MK Jordan, and DW Lynch. 1979. Effects of inhalation exposures and intraperitoneal injections of methyl n-amyl ketone on MULTFRFI response rates in rats. *Toxicol App Pharmacol* 49:407-416.

ChemFinder.com. 2004. Methyl n-amy ketone. ChemFinder.com Database and Internet Searching. http://chemfinder.cambridgesoft.com/result.asp, accessed March 15, 2007.

Cometto–Muñiz, JE, and WS Cain. 1991. Nasal pungency, odor, and eye irritation thresholds for homologous acetates. *Pharmacol Bichem Behav* 39:983-989.

Cometto–Muñiz, JE. 1993. Personal communication, The John B. Pierce Laboratory, New Haven Connecticut.

Cometto–Muñiz, JE, and WS Cain. 1993. Efficacy of volatile organic compounds in evoking nasal pungency and odor. *Arch Environ Health* 48: 309–314.

Cometto–Muñiz, JE, WS Cain, MH Abraham, and JMR Gola. 1999.Chemosensory detectability of 1-butanol and 2-heptanone singly and in binary mixtures. *Physiol Behav* 67: 269-276.

Hessamedin, A and WL Silver. 2000. Evidence for nicotinic acetylcholine receptors on nasal trigeminal nerve endings of the rat. *Chem Senses* 25:61-66.

Hazardous Substance Data Bank (HSDB). 2006. Methyl n-Amyl Ketone. United States National Library of Medicine, http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB, accessed March 15, 2007.

Johnson, BL, JV Setzer, TR Lewis, and RW Hornung. 1979. An electrodiagnostic study of the neurotoxicity of methyl n-amyl ketone. *Am Ind Hyg* Assoc J 39:866-872.

Lynch, DW, TR Lewis, WJ Moorman, HB Plotnick, RL Schuler, AW Smallwood, and C Kommineni.

1981. Inhalation toxicity of methyl n-amyl ketone (2-heptanone) in rats and monkeys. *Toxicol Appl Pharmacol* 58: 341-352.

Nagata, Y. 2003. Measurement of odor threshold by triangle odor bag method. Odor Measurement Review, Japan Ministry of the Environment. 118-127.

Texas Commission on Environmental Quality (TCEQ). 2006. Guidelines to develop effects screening Levels, Reference Values, and Unit Risk Factors. RG-442. Chief Engineer's Office, Austin, TX.

Texas Commission on Environmental Quality (TCEQ). (2015). Approaches to derive odor-based values. Texas Commission on Environmental Quality. Office of the Executive Director, Austin, TX.

United States Environmental Protection Agency. (USEPA 1992). Reference Guide to Odor Thresholds for Hazardous Air Pollutants Listed in the Clean Air Act Amendments of 1990. EPA600/R-92/047. Office of Research and Development, Washington, D.C.

United States Environmental Protection Agency. (USEPA 1994). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Washington, DC: U.S. *Environmental Protection Agency*. EPA/600/8-90/066F.

Unpublished data. Eastman Kodak Company. 1964.

Unpublished data. Eastman Kodak Company. 1996.

5.2 Other Studies and Documents Reviewed by the TS

Abraham, MH, J Andonian–Haftvan, JE Cometto–Muñiz, and Cain. 1996. An analysis of nasal irritation thresholds using a new solvation equation. *Fundam Appl Toxicol* 31:71–76.

Amoore, JE, E Hautala. 1983. Odor as an Aid to Chemical Safety: Odor Thresholds Compared with Threshold Limit Values and Volatilities for 214 Industrial Chemicals in Air and Water Dilution. *J. Appl. Toxicol.* 3(6):272-290.

Barber, ED, KR Miller, MI Banton, and RM Vijayaraj. 1999. The lack of binding of methyl-n-amyl

ketone (MAK) to rat liver DNA as demonstrated by direct binding measurements, and P-

postlabeling techniques. *Mutation Research* 442:133-147.

Cometto–Muñiz, JE, and WS Cain. 1991. Sensory irritation and pulmonary irritation of n-methyl ketones: receptor activation mechanisms and relationships with threshold limit values. *Arch Toxicol* 68: 193-202.

Cometto–Muñiz, JE, and WS Cain. 1994. Perception of odor and nasal pungency from homologous series of volatile organic compounds. *Indoor Air* 4: 140-145.

Cometto–Muñiz, JE, and WS Cain. 1995. Relative sensitivity of the ocular trigeminal, nasal trigeminal, and olfactory systems to airborne chemicals. *Chem Senses* 20:191–198.

Gaunt, IF, FMB Carpanini, MG Wright, P Grasso, and SD Gangolli. 1972. Short-term Toxicity of Methyl Amyl Ketone in Rats. *Food and Cosmetic Toxicol* 10:625-636.

Smyth, HF, CP Carpenter, CS Weil et al. 1962. Range-Finding Toxicity Data: List VI. *Am Ind Hyg Assoc J* 23:95-107.

Specht, H, JW Miller, PJ Valaer, and RR Sayers. 1940. Acute Response of Guinea Pigs to the Inhalation of Ketone Vapors. *NIH Bulletin.* No. 176:1-166.

Ziemer, PD, J Woo, and T Anagnostou. 2000. Study of odor qualification of solvents used in coating compositions. *J Coat Tech* 72(907):97-102.