UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: July 25, 2006

ACTION MEMORANDUM

SUBJECT: Inert Reassessments: Six Exemptions from the Requirement of a Tolerance for Methyl *n*-Amyl Ketone (CAS Reg. No. 110-43-0), Methyl Ethyl Ketone (CAS Reg. No. 78-93-3), and Methyl Isobutyl Ketone (CAS Reg. No. 108-10-1)

FROM: Pauline Wagner, Chief Pauline Wagner 7/27/06
Inert Ingredient Assessment Branch
Registration Division

TO: Lois A. Rossi, Director
Registration Division

I. FQPA REASSESSMENT ACTION

Action: Reassessment of six inert ingredient exemptions from the requirement of a tolerance. Current exemptions are to be maintained.

Chemical: Methyl *n*-amyl ketone, methyl ethyl ketone, and methyl isobutyl ketone
CFR: 40 CFR 180.910, 920 and 930
CAS #: 110-43-0, 78-93-3 and 108-10-1

Table 1. Tolerance Exemptions Expression

40 CFR	Inert Ingredients	Limits	Uses (Pesticidal)	CAS Reg. No. and 9 CI Name
180.910	Methyl *n*-amyl ketone (CAS Reg. No. 110-43-0)	None	Solvent, cosolvent	110-43-0 2-Heptanone
	Methyl isobutyl ketone		Solvent	108-10-1 2-Pentanone, 4-methyl-
180.920	Methyl ethyl ketone	None	Surfactant[a]	78-93-3 2-Butanone
	Methyl isobutyl ketone		Solvent, cosolvent	108-10-1 2-Pentanone, 4-methyl-

40 CFR	Inert Ingredients	Limits	Uses (Pesticidal)	CAS Reg. No. and 9 CI Name
180.930	Methyl *n*-amyl ketone (CAS Reg. No. 110-43-0)	None	Solvent, cosolvent	110-43-0 2-Heptanone
	Methyl isobutyl ketone		Solvent, cosolvent	108-10-1 2-Pentanone, 4-methyl-

a. Note: The description in 180.920 of MEK's use as a "surfactant" is incorrect. A Federal Register notice will be issued in the future to correct the CFR so the use of MEK is correctly described as a "Solvent".

Use Summary: MEK, MAK, and MIBK are used primarily as solvents in the manufacture of a wide variety of consumer products and as chemical intermediates, such as adhesives, magnetic tapes, printing inks, de-greasing and cleaning fluids, antioxidants, perfumes, lacquers paint removers, cleaning fluids, acrylic coatings, pharmaceuticals, and resins. As inert ingredients, MEK, MAK, and MIBK are used as solvents, cosolvents, and surfactants in pesticide formulations.

List Reclassification Determination: The current List Classification for MEK, MAK, and MIBK is 3. Because EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to these chemicals when used as solvents, cosolvents in pesticide formulations applied to animals, the List Classification for MEK, MAK, and MIBK will change from List 3 to List 4B.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the six exemptions from the requirement of a tolerance for the inert ingredients methyl *n*-amyl ketone (CAS Reg. No. 110-43-0), methyl ethyl ketone (CAS Reg. No. 78-93-3), and methyl isobutyl ketone (CAS Reg. No. 108-10-1). I consider the six exemptions established in 40 CFR 180.910, 920 and 930 to be reassessed for purposes of FFDCA's section 408(q) as of the date of my signature, below. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.

Lois A. Rossi

Lois A. Rossi, Director
Registration Division

Date: July 31, 2006

CC: Debbie Edwards, SRRD
Joe Nevola, SRRD

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

July 27, 2006

MEMORANDUM

SUBJECT: Reassessment of the Six Exemptions from the Requirement of a Tolerance for Methyl *n*-Amyl Ketone (CAS Reg. No. 110-43-0), Methyl Ethyl Ketone (CAS Reg. No. 78-93-3), and Methyl Isobutyl Ketone (CAS Reg. No. 108-10-1)

FROM: Karen Angulo
Inert Ingredient Assessment Branch (IIAB)
Registration Division (7505P)

TO: Pauline Wagner, Chief
Inert Ingredient Assessment Branch (IIAB)
Registration Division (7505P)

Background

Attached is the science assessment for methyl *n*-amyl ketone (MAK) (CAS Reg. No. 110-43-0), methyl ethyl ketone (MEK) (CAS Reg. No. 78-93-3), and methyl isobutyl ketone (MIBK) (CAS Reg. No. 108-10-1). This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of MEK, MAK, and MIBK. The purpose of this document is to reassess the six existing exemptions from the requirement of a tolerance for residues of MEK, MAK, and MIBK when used as inert ingredients in pesticide formulations as required under the Food Quality Protection Act (FQPA).

Executive Summary

This report evaluates MEK, MAK, and MIBK, pesticide inert ingredients for which six exemptions from the requirement of tolerance exist under 40 CFR 180.910, 920, and 930 when they are used as solvents/cosolvents in pesticide formulations.

MEK, MAK, and MIBK have been well studied and sufficient toxicity data and information are available from a variety of publicly available sources. The primary sources of data for this assessment are the U.S. EPA's Integrated Risk Information System (IRIS), the U.S. Agency for Toxic Substances and Disease Registry (ATSDR), U.S. EPA's High Production Volume (HPV) Challenge Program, the World Health Organization's International Programme on Chemical Safety (INCHEM), and the Organization for Economic Cooperation and

Development's (OECD) Screening Information Data Sets (SIDS). This document provides only a brief summary of conclusions from these documents and the reader is referred to these sources for the full assessments.

MEK, MAK, and MIBK are used primarily as solvents in the manufacture of a wide variety of consumer products and as chemical intermediates. The U.S. Food and Drug Administration (FDA) permits the use of MEK, MIBK and MAK as food additives (synthetic flavoring substances and adjuvants) for direct addition to food for human consumption. MEK, MAK, and MIBK occur naturally in a wide variety of foods, and all are readily metabolized in the body. MEK, for example is rapidly and nearly completely metabolized in the body and much of it is transformed into simple compounds such as carbon dioxide and water.

MEK, MAK, and MIBK have a low order of toxicity following acute and subchronic oral, dermal, and inhalation exposure. Mutagenicity/genotoxicity studies have been consistently negative for these chemicals. There is some evidence of carcinogenic activity for MIBK in animal studies but at exposure levels higher than anticipated from the use of this chemical in pesticide products. Animal studies show that developmental effects were observed at exposures of approximately of 3,000 ppm, a level that also is associated with maternal toxicity.

Dietary (food and drinking water) exposures of concern are not anticipated from the use of MEK, MAK, and MIBK as inert ingredients in pesticide products, considering their volatile nature and ready biodegradation in the environment. Dermal exposures of concern are not expected from applications of pesticide products containing these chemicals in residential settings because of the chemicals' volatile natures. The results of conservative E-FAST screening level modeling show that inhalation exposures of concern from residential uses are not anticipated from the use of MEK, MAK, and MIBK as inert ingredients in pesticide products.

Considering their low order of toxicity, ready biodegradation in the environment, natural occurrence in a wide variety of foods, ready metabolism in the body, and safe history of use as a food additive, no dietary or residential risks of concern are identified for MEK, MAK, and MIBK when used as inert ingredients in pesticide products.

Taking into consideration all available information on MAK, MEK, and MIBK, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to MAK, MEK, and MIBK when considering exposure through food commodities and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the six exemptions from the requirement of a tolerance established for residues of MAK (under 40 CFR 180.910 and 930), MEK (under 40 CFR 180.920), and MIBK (under 40 CFR 180.910, 920, and 930) can be considered reassessed as safe under section 408(q) of the Federal Food, Drug, and Cosmetic Act (FFDCA).

I. Introduction

This report provides a qualitative assessment of the six tolerance exemptions for the inert ingredients MEK, MAK, and MIBK.

II. Use Information

A. Pesticide Uses

The tolerance exemption expressions for MAK, MEK, and MIBK are presented below in Table 1.

Table 1. Tolerance Exemptions

CFR Citation				CAS Reg. No. and CAS Name
40 CFR	**Inert Ingredients**	**Limits**	**Uses**	
180.910[a]	Methyl *n*-amyl ketone (CAS Reg. No. 110-43-0)	None	Solvent, cosolvent	110-43-0 2-Heptanone
	Methyl isobutyl ketone		Solvent	108-10-1 2-Pentanone, 4-methyl-
180.920[b]	Methyl ethyl ketone		Surfactant[d]	78-93-3 2-Butanone
	Methyl isobutyl ketone		Solvent, cosolvent	108-10-1 2-Pentanone, 4-methyl-
180.930[c]	Methyl *n*-amyl ketone (CAS Reg. No. 110-43-0)		Solvent, cosolvent	110-43-0 2-Heptanone
	Methyl isobutyl ketone		Solvent, cosolvent	108-10-1 2-Pentanone, 4-methyl-

a. Residues listed in 40 CFR 180.910 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities (RACs) after harvest.
b. Residues listed in 40 CFR 180.920 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.
c. Residues listed in 40 CFR 180.920 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals.
d. Note: The description of the use of MEK in 180.920 as a "surfactant" is incorrect. A Federal Register notice will be issued in the future to correct the CFR so the use of MEK is correctly described as a "Solvent".

B. Other Uses.

MEK, MAK, and MIBK are used primarily as solvents in the manufacture of a wide variety of consumer products and as chemical intermediates, such as adhesives,

magnetic tapes, printing inks, de-greasing and cleaning fluids, antioxidants, perfumes, lacquers paint removers, cleaning fluids, acrylic coatings, pharmaceuticals, and resins (HSDB, 2006).

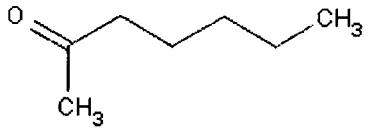
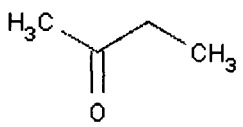
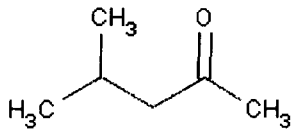
The FDA permits the use of MEK, MIBK and MAK under 40 CFR part 21 (See Table 2).

Table 2. Food Additives

Name	21 CFR	Use
MEK, MAK, and MIBK	172.515	Food additives permitted for direct addition to food for human consumption; synthetic flavoring substances and adjuvants.
MEK and MIBK	175.105	Indirect food additives; components of adhesives.
MEK	175.320	Indirect food additives; resinous and polymeric coatings for polyolefin films.

III. Physical and Chemical Properties.

Physical and chemical characteristics of MAK, MEK, and MIBK are found in Table 3.

Table 3. Physical and Chemical Properties				
	Methyl *n*-amyl ketone (MAK)	**Methyl ethyl ketone (MEK)**	**Methyl isobutyl kethone (MIBK)**	**Reference**
Structure				ChemIDPlus, 2006
CAS Number	110-43-0	78-93-3	108-10-1	ChemIDPlus, 2006
Molecular Formula	C_7-H_{14}-O	C_4-H_8-O	C_6-H_{12}-O	HSDB, 2006
Molecular Weight	114.18	72.11	100.16	HSDB, 2006
Synonyms	Amyl methyl ketone; Butylacetone; Methyl n-pentyl ketone; Pentyl methyl ketone	Acetone, methyl-; Ethyl methyl ketone; Ketone, ethyl methyl; Methyl acetone; Butanone	4-Methyl-2-pentanone, Hexone, Isopropylacetone, 2-Methyl-4-pentanone, Isobutyl methyl ketone	ChemIDPlus, 2006
Odor	Penetrating fruity odor	Moderately sharp, fragrant mint- or acetone-like odor.	Pleasant odor; faint ketonic and camphor odor	HSDB, 2006
Physical State	Colorless to white liquid	Colorless liquid	Colorless liquid	HSDB, 2006
Melting Point	-35.5°C	-86°C	-85°C	HSDB, 2006
Boiling Point	151.5°C @ 760 mm Hg	79.6°C	115°C @ 760 mm Hg	HSDB, 2006
Water Solubility	4,300 mg/L @ 25°C	2.23×10^5 mg/L @ 25°C	19,000 mg/L @ 25°C	ChemIDPlus, 2006
Other Solubility	Soluble in alchohol and ether	Soluble in alcohol, ether, acetone and benzene	Soluble in alcohol, ether, acetone, benzene, and chloroform.	HSDB, 2006
Vapor Pressure	1.6 mm Hg @ 25°C	90.6 mm Hg @ 25°C	19.9 mm Hg @ 25°C	ChemIDPlus, 2006; HSDB, 2006
Log K_{ow}	1.98	0.29	1.31	HSDB, 2006
Henry's Law Constant	1.69×10^{-4} atm-m^3/mole	5.69×10^{-5} atm-m^3/mole	1.38×10^{-4} atm-m^3/mole	ChemIDPlus, 2006

IV. Hazard Assessment for Methyl Ethyl Ketone (MEK)

A. Hazard Profile -- MEK

MEK has been well studied and sufficient toxicity data and information are available from a variety of publicly available sources. The primary sources of data for this assessment are the reports on MEK from U.S. EPA's Integrated Risk Information System (IRIS, 2003) and the U.S. Agency for Toxic Substances and Disease Registry (ATSDR; 1992). Other sources of information used in this assessment include the Hazardous Substances Data Bank (HSDB) and a Screening Information Data Set (SIDS) on MEK that was prepared by EPA and submitted under the OECD SIDS High Production Volume Chemicals Program (OECD, 1997). This document provides only a brief summary of conclusions from the ATSDR and IRIS documents and the reader is referred to these sources for the full assessments.

The OECD SIDS (1997) found methyl ethyl ketone to be a "low priority for further work." The following excerpt is directly from the SIDS: "MEK has been shown to be of a low order of toxicity following acute oral, dermal, and inhalation exposure. Contact with the eyes may produce irritation. MEK has not been shown to produce skin sensitization. No significant signs of toxicity were seen following repeated inhalation exposure of rats to MEK at high concentrations. MEK and its metabolic surrogate, 2-butanol, do not appear to present significant risk of adverse reproductive or developmental effects. MEK has not been shown to have any neurotoxic potential. MEK has been consistently negative in genotoxicity studies, both *in vitro* and *in vivo*."

B. Metabolism and Pharmacokinetics – MEK

According to IRIS (2003), animal studies suggest that MEK is well absorbed during inhalation, dermal, and oral exposures, but it is rapidly and nearly completely metabolized in the body. Considering its high vapor pressure, inhalation is the main route of exposure to MEK. A small percentage of an absorbed dose is exhaled as unchanged MEK or excreted in urine as 2,3-butanediol. Much of the dose is transformed to simple compounds such as carbon dioxide and water.

C. Toxicological Data -- MEK

Acute Toxicity-- MEK

Table 4 provides a summary of acute toxicity data reported in ATSDR (1992). MEK has a low order of toxicity following acute oral, dermal, and inhalation exposure.

Table 4. Summary of Acute Toxicity Data for MEK

Parameter		Toxicity Value	Reference
Oral	Rat and Mouse	No deaths at 1,080 mg/kg	Brown and Hewitt 1984, and Hewitt et al. 1983, both as cited in ATSDR, 1992
	Mouse	LD_{50} = 4,044 mg/kg	Tanii et al.1986, as cited in ATSDR, 1992
Inhalation	Rat (8-hour)	LC_{50} = 8,000 ppm	Smyth et al. 1962, as cited in ATSDR, 1992
	Mouse (4-hour)	No deaths at 2,438 ppm	De Ceaurriz et al. 1983, as cited in ATSDR, 1992
Irritation	Severe upper respiratory tract irritation was found after a few days in rats exposed to 10,000 ppm, 8 hours/day (Altenkirch et al. 1978a, as cited in ATSDR, 1992).		

Repeated Dose Toxicity – MEK

Considering its high vapor pressure, inhalation is the main route of exposure to MEK. In a 90-day inhalation study, exposure of rats to concentrations of MEK at 5,000 ppm or less caused no signs of upper respiratory tract irritation or other respiratory effects (Cavender et al. 1983, as cited in ATSDR, 1992).

Neurotoxicity – MEK

Neurological effects have been observed in animals exposed to high levels of MEK. For example, ATSDR (1992) reported the following results from inhalation, oral, and dermal toxicity studies on MEK. In an inhalation toxicity study on the mouse, exposure to MEK at concentrations greater than or equal to 1,602 ppm for 4 hours resulted in a dose-related reduction in the duration of immobility in a "behavioral despair" swimming test (De Ceaurriz et al. 1983, as cited in ATSDR, 1992). In another inhalation toxicity study, male Sprague-Dawley rats exposed continuously to 1,125 ppm MEK for periods of 5 months or less showed no signs of peripheral neuropathy following histological examination (Saida et al. 1976, as cited in ATSDR, 1992).

In an oral toxicity study, no effect was observed in neurobehavioral tests including in rats treated by gavage with MEK at a time-weighted average dose of 173 mg/kg/day for 90 days (Ralston et al. 1985, as cited in ATSDR, 1992). In a dermal toxicity study, no clinical signs of neurotoxicity were observed when l-2 mL of undiluted MEK was applied in increasing amounts to shaved areas on the backs of guinea pigs 5 days/week for 31 weeks or less (Eastman Kodak 1978, as cited in ATSDR, 1992).

Mutagenicity and Genotoxicity – MEK

IRIS (2003) reported the following: "MEK has not exhibited mutagenic activity in a number of conventional short-term test systems. *In vitro* tests showed that MEK was not

genotoxic in the Salmonella (Ames) assay (with or without metabolic activation), the L5178/TK$^{+/-}$ mouse lymphoma assay, and the BALB/3T3 cell transformation assay, and did not induce unscheduled DNA synthesis in rat primary hepatocytes, chromosome aberrations, or sister chromatic exchange (Florin et al., 1980; Douglas et al., 1980; O'Donoghue et al., 1988; NTP, undated; Zeiger et al., 1992). No induction of micronuclei was found in the erythrocytes of mice (O'Donoghue et al., 1988) or hamsters (WHO, 1992) after intraperitoneal injection with MEK. The only evidence of mutagenicity was mitotic chromosome loss at a high concentration in a study on aneuploidy in the diploid D61, M strain of the yeast *Saccharomyces cerevisiae* (Zimmermann et al., 1985); the relevance of this positive result to humans is unknown. In general, studies of MEK yielded little or no evidence of mutagenicity. SAR analysis suggests that MEK is unlikely to be carcinogenic based on the absence of any structural alerts indicative of carcinogenic potential (Woo et al., 2002)."

Reproductive/Developmental Toxicity – MEK

In a study reported in IRIS (2003) and also reported by NTP (1990), Schwetz et al. (1991) exposed groups of mice via the inhalation route to MEK concentrations of 0, 398±9, 1,010±28, or 3,020±79 ppm (0, 1,174±27, 2,980±83, or 8,909±233 mg/m^3) for 7 hours/day on gestation days 6–15. Dams were sacrificed on gestation day 18. Developmental and maternal toxicity levels were established at 3,020 ppm based on a small decrease in fetal weight among males, increased incidence of misaligned sternebrae, and an increase in the maternal liver-to-body-weight ratio.

Another study reported similar developmental results (Deacon et al., 1981, as cited in IRIS, 2003). Groups of rat dams were exposed to MEK concentrations of 0, 400, 1,000, or 3,000 ppm (7 hours/day on gestation days 6–15). This study found maternal toxicity (decreased weight gain) and fetal toxicity (increased incidence of skeletal variations) at 3,005 ppm (LOAEL) but not at 1002 ppm (NOAEL).

V. Hazard Assessment for Methyl n-Amyl Ketone (MAK)

A. Hazard Profile -- MAK

The data and information on MAK is from a Test Plan submitted to the Agency in 2002 under EPA's High Production Volume (HPV) Challenge Program. The goal of the HPV program is to collect and make publicly available a complete set of baseline health and environmental effects data on those chemicals that are manufactured in, or imported into, the United States in amounts equal to or exceeding one million pounds per year. Industry sponsors volunteer to evaluate the adequacy of existing data and to conduct tests where needed to fill the gaps in the data, and EPA (and the public) has an opportunity to review and comment on the sponsors' robust summary report. A robust summary has been submitted for MAK, and EPA has reviewed the submission. The relevant data have been made part of this assessment, below. The reader is referred to the HPV submission for the full robust summary.

B. Metabolism and Phamacokinetics -- MAK

The National Institute for Occupational Safety and Health (NIOSH, as cited in HPV, 2002) conducted a 10-month inhalation study of rats and monkeys exposed (whole-body) to MAK (97%) vapors at 0, 100, or 1000 ppm for 6 hours/day 5 days/week for 10 months. The results indicated that the liver contained the most radioactivity with the next highest levels detected in the kidney, pancreas, and lungs. "Excretion of MAK into the urine and feces peaked at 12 hours and remained relatively constant through 48 hours. Fecal excretion through 72-hours only accounted for 2% of the administered dose."

C. Toxicological Data -- MAK

Acute Oral – MAK

Table 5 provides a summary of acute toxicity data reported in the MAK HPV submission (HPV, 2002). MAK has a low order of toxicity following acute oral and inhalation exposure.

Table 5. Summary of Acute Toxicity Data for MAK

Parameter		Toxicity Value	Reference
Oral	Rat	LD_{50} = 1,600 mg/kg.	Eastman Kodak Company, as cited in HVP, 2002
	Mouse	$LD_{50} \geq$ 1600 mg/kg.	
Inhalation	Rat (6-hour)	LC_{50} = 4000 ppm	

Repeat-dose – MAK

NIOSH (as cited in HPV, 2002) conducted a repeat-dose inhalation study where groups of 50 rats and 8 monkeys were exposed (whole-body) to MAK (97%) vapors at 0, 100, or 1000 ppm for 6 hours/day 5 days/week for 10 months. "Both species tolerated the exposures without developing overt signs of toxicity or alterations in weight gains or clinical chemistries". No gross or microscopic changes in any examined organ or tissue were observed. The NOAEL for both species was determined to be 1025 ppm.

In a 13-week oral gavage study (Gaunt, et. al., as cited in HPV, 2002), rats were administered 0, 20, 100, or 500 mg/kg/day of MAK (98%) in corn oil. The NOEL was determined to be 20 mg/kg/day due to 1) an increase in urine cellularity in males in the mid- and high dose level groups, 2) changes in relative kidney weight in males in the mid- and high-dose level groups, and 3) changes in relative liver weights in both sexes in the high dose level groups. "Despite the reported organ weights changes, no histological alterations were noted in any tissue. No serum biochemical changes were noted that might also be reflective of renal or hepatic toxicity." While this study reported kidney and liver effects in rats, the applicability to humans is questionable since rats are sensitive to liver and kidney changes.

Mutagenicity/Genotoxicity – MAK

An *in vitro* Ames mutagenicity study on *Salmonella typhimurium* strains TA98, 100, 1535, 1537, and 1538 was conducted with MAK (99%) at a maximum concentration of 5000 µg/plate. This chemical was negative both with and without activation (Microbiological Associates, Inc., as cited in HPV, 2002).

An in vitro mammalian chromosomal aberration assay on Chinese hamster ovary cells (CHO) was conducted with up to 1200 µg/mL of MAK (99.8%). This chemical was negative both with and without activation (Covance Laboratories Inc., as cited in HPV, 2002).

Reproductive/Developmental Toxicity -- MAK

In a combined reproduction/developmental study (Eastman Kodak Company, as cited in HPV, 2002), rats were exposed (whole-body) via inhalation to 0, 80, 400, or 1000 ppm of MAK (>99%) vapor 6 hrs/day, 7 days/week for 50 days (males) or 34-47 days (females – through Day 19 of gestation). A dose responsive reduction in activity was noted in the high- and mid-dose animals. "Animals appeared to become acclimated as this reduction went from moderate, to minor, to minimal by study conclusion. Males in the high dose group exhibited a decrease in food consumption during days 0-7 only. There was no effect on body weight in either sex, although mid-dose females exhibited less of a weight change during 0-7 days of gestation." There were no exposure-related effects on litter parameters or in any of the examined organs. There were "no treatment-induced changes in pup clinical signs or abnormalities, or weight gains at any measured time-period." The NOEL from maternal toxicity was determined to be 80 ppm and the NOEL for developmental toxicity was determined to be 1000 ppm. It was concluded from the study results that the test material did not induce reproductive or developmental toxicity.

V. Hazard Assessment for Methyl Isobutyl Ketone (MIBK)

A. Hazard Profile -- MIBK

MIBK has been well studied and sufficient toxicity data and information are available from a variety of publicly available sources. The primary sources of data for this assessment are a SIDS on MIBK that was prepared by EPA (OECD, 1996), EPA's 2003 IRIS report on MIBK, and two reports on MIBK from the World Health Organization's International Programme on Chemical Safety (INCHEM, 1990 and 1991). This document provides only a brief summary of conclusions from the INCHEM and IRIS documents and the reader is referred to these sources for the full assessments.

B. Metabolism and Phamacokinetics -- MIBK

According to INCHEM (1991): "MIBK is absorbed in animals via inhalation, ingestion, and through the skin. It is widely distributed throughout the body. MIBK is readily metabolized to water-soluble excretory products and can induce metabolic activation in the liver. The urine is the major route of excretion for metabolites."

C. Toxicological Data -- MIBK

Acute Oral – MIBK

Table 6 provides a summary of acute toxicity data reported in the INCHEM (1991) MIBK report. MIBK has a low order of toxicity following acute oral and inhalation exposure.

Table 6. Summary of Acute Toxicity Data for MIBK

Parameter		Toxicity Value	Reference
Oral	Rat	LD_{50} = 4600 mg/kg.	Batyrova, 1973, as cited in WHO, 1990
	Mouse	$LD_{50} \geq$ 2850 mg/kg.	
Inhalation	Rat (4-hour)	LC_{50} = 2 - 16.4 g/m^3	Smyth et al., as cited in WHO, 1990
	Mouse (2 hour)	LC_{50} = 20.5 g/m^3	Batyrova, 1973, as cited in WHO, 1990

Repeat-dose – MIBK

Dodd & Eisler, 1983 (as cited in INCHEM, 1990), reported that in 90-day inhalation studies on rats and mice, concentrations of up to 4100 mg/m^3 (1000 ppm) did not result in significant toxicity, though compound-related reversible morphological changes were reported in the liver and kidney.

According to Microbiological Associates, 1986 (as cited in INCHEM, 1990), MIBK was administered to rats by oral gavage at levels of 0, 50, 250, or 1000 mg/kg daily for 13 weeks. Increased liver and kidney weights were observed for males and females at 1000 mg/kg per day, but no corresponding histopathological lesions were present in the liver. The effects seen at 1000 mg/kg per day were present to a significantly lesser extent in the females and males fed 250 mg/kg per day. No effects were observed at 50 mg/kg per day (NOEL).

Mutagenicity/Genotoxicity – MIBK

MIBK was negative in a Salmonella reverse mutation test, a mouse lymphoma assay, a cell transformation assay using BALB/3T3 cells, an unscheduled DNA synthesis assay, and a mouse bone marrow micronucleus test (OECD, 1996).

Carcinogenicity – MIBK

The National Toxicology Program (NTP, 2005) reported the results of a recent carcinogenicity study on MIBK and provided this summary of the conclusions: "Under the conditions of these 2-year studies, there was *some evidence of carcinogenic activity* of methyl isobutyl ketone in male F344/N rats based on increased incidences of renal tubule neoplasms. Increased incidences of mononuclear cell leukemia in 1,800 ppm male F344/N rats may have been related to methyl isobutyl ketone exposure. There was *equivocal evidence of carcinogenic*

activity of methyl isobutyl ketone in female F344/N rats based on the occurrence of renal mesenchymal tumors in the 1,800 ppm group. There was *some evidence of carcinogenic activity* of methyl isobutyl ketone in male and female $B6C3F_1$ mice based on increased incidences of liver neoplasms."

Reproductive/Developmental Toxicity -- MIBK

According to OECD (1996), "In inhalation developmental toxicity studies in rats and mice, maternal toxicity and fetotoxicity were seen at 3000 ppm. Effects in the dams included decreased body weight gain, increased liver and kidney weights, decreased food consumption, and in mice, maternal deaths. Reduced fetal body weights and delayed ossification were noted in both species and increased resorptions were noted for mice. 1000 ppm was considered to be the NOEL for both maternal animals and offspring." This same study was summarized in IRIS (2003).

VI. Special Considerations for Infants and Children

MEK, MAK, and MIBK all have sufficient data to evaluate developmental toxicity via the inhalation route of exposure, which is the main route of exposure for these chemicals considering their volatile natures. Developmental effects were observed only at high dose levels and in the presence of maternal toxicity:

- For MEK, an inhalation developmental toxicity study found maternal toxicity (decreased weight gain) and fetal toxicity (increased incidence of skeletal variations) at 3,005 ppm (LOAEL) but not at 1,002 ppm (NOAEL) (Deacon et al., 1981, as cited in IRIS, 2003).
- For MAK, an inhalation developmental toxicity study reported that the NOEL from maternal toxicity was 80 ppm and the NOEL for developmental toxicity was 1,000 ppm (Eastman Kodak Company, as cited in HPV, 2002). There were no exposure-related effects on litter parameters or in any of the examined organs.
- For MIBK, maternal toxicity and fetotoxicity were seen at 3,000 ppm in inhalation developmental toxicity studies in rats and mice, and 1000 ppm was considered to be the NOEL for both maternal animals and offspring (OECD, 1996).

Based on this information there is no concern, at this time, for increased sensitivity to infants and children to MAK, MEK, and MIBK when used as an inert ingredient in pesticide formulations. For the same reason, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

V. Environmental Fate Characterization and Drinking Water Considerations

According to ATSDR (1992), MEK is expected to rapidly volatilize from surface water and moist or dry soils to the atmosphere. The half-life of MEK in the atmosphere is approximately 1 day or less because it is expected to undergo a vapor-phase reaction with photochemically produced hydroxyl radicals. In water, MEK will undergo microbial degradation under both aerobic and anaerobic conditions. MEK is not expected to bioconcentrate in fish and aquatic organisms.

A summary of the environmental fate characteristics of MAK is found in the HSDB (2006). Volatilization from both moist and dry soils may be a significant fate process for MAK and it may biodegrade in soil under aerobic conditions. If released to water, MAK is expected to volatilize to the atmosphere. In the atmosphere, MAK will undergo gas-phase reaction with photochemically produced hydroxyl radicals, and the estimated half-life for this process is 1.9 days. The estimated half-life for volatilization from a model river is 8.4 hrs. MAK is expected to biodegrade under aerobic conditions in aquatic systems. MAK is not expected to significantly bioconcentrate in fish and aquatic organisms. (HSDB, 2006). In addition, studies in the HPV submission for MAK report that it is expected to rapidly degrade in the atmosphere (Wallington and Kurylo, 1987, as cited in HPV, 2002) and is readily biodegradable (Eastman Kodak Company, 1997, as cited in HPV, 2002).

According to OECD (1996), "MIBK is not expected to persist in the environment. In water, MIBK has been shown to be readily biodegradable. MIBK is expected to volatilize rapidly from water or soil, where rapid photodegradation would occur. Bioconcentration is not expected to be an important fate process."

Considering the physical-chemical properties and ready biodegradation in the environment, contributions of concern to drinking water are not expected from the use of MEK, MAK, and MIBK as inert ingredients in pesticide products.

VI. Exposure Assessment

MEK, MAK, and MIBK occur naturally in many foods. MEK is a natural component of many foods including raw chicken, milk, nuts, cheese, bread dough, and nectarines. It has been detected in dried beans, split peas, lentils (148, 110, and 50 ppm) southern peas, winged beans, and soybeans. MEK is emitted from various evergreen trees (HSDB, 2006, and ATSDR, 1992). MAK is a natural component of many foods including roasted filberts, baked potatoes, blue cheese, Beaufort (Gruyere) cheese, fried bacon, clove essential oil, chickpeas, fried chicken, swiss cheese, butter, milk, cream, white bread, soybeans, peaches, and orange juice (HSDB, 2006). MIBK has been detected in foods such as baked potatoes, scrambled eggs, cured beef and cured chicken, salt-fermented anchovies and shrimp (HSDB, 2006).

Dietary (food and drinking water) exposures of concern are not anticipated from the use of MEK, MAK, and MIBK as inert ingredients in pesticide products considering their volatile nature and ready biodegradation in the environment. Their volatile nature will also reduce the potential for dermal exposures from applications of pesticide products containing these chemicals in residential settings.

The volatile nature of MEK, MAK, and MIBK increases the potential for acute inhalation exposures from residential use pesticide products. The E-FAST screening level model was used to assess the potential for inhalation exposure of MEK. MEK was selected rather than MAK or MIBK because it is has the highest vapor pressure (90.6 mm Hg @ 25°C). E-FAST was developed by EPA's Office of Pollution, Prevention and Toxics as a tool to estimate concentrations of chemicals released from consumer products. Modeled estimates of

concentrations and doses are designed to reasonably overestimate exposures for use in a screening level assessment. For MEK, E-FAST's aerosol paint scenario was selected because it estimates potential inhalation exposure over 20 minutes of aerosol paint use in an enclosed utility room. The Agency considers an acute inhalation exposure to be a single event occurring over a period of less than 24 hours. In this case, the E-FAST generated estimates of exposure are expected to be greater than what is reasonably anticipated from the use of MEK as an inert ingredient in residential-use pesticide products. Appendix A provides the model runs from E-FAST.

The average concentration of MEK in aerosol paint products used in the E-FAST model was 10%, which was calculated by averaging the MEK concentrations in many products. The results of the model run (Appendix A) show a peak concentration potential dose (Cp_{pot}) of 299 ppm (884 mg/m^3).

VII. Aggregate Exposures

In examining aggregate exposure, the FFDCA section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other nonoccupational exposures, including drinking water (ground water or surface water) and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

For MAK, MEK, and MIBK, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the lack of human health concerns associated with exposure to MAK, MEK, and MIBK as inert ingredients in pesticide formulations.

VIII. Cumulative Exposure

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to MAK, MEK, and MIBK and any other substances and, these materials do not appear to produce toxic metabolites produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that MEK, MAK, and MIBK have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

IX. Human Health Risk Characterization

MEK, MAK, and MIBK occur naturally in a wide variety of foods. All are readily metabolized in the body. MEK, for example, is rapidly and nearly completely metabolized in the body and much of it is transformed into simple compounds such as carbon dioxide and water.

MEK, MAK, and MIBK have a low order of toxicity following acute and subchronic oral, dermal, and inhalation exposure. Mutagenicity/genotoxicity studies have been consistently negative for these chemicals. Animal studies may show some evidence of carcinogenic activity for MIBK but at exposure levels higher than anticipated from the use of this chemical in pesticide products. Animal studies show that developmental effects were observed at approximately 3,000 ppm, a level that also is associated with maternal toxicity (NOELs are approximately 1,000 ppm).

Dietary (food and drinking water) exposures of are not anticipated from the use MEK, MAK, and MIBK as inert ingredients in pesticide products, considering their volatile nature and ready biodegradation in the environment. The volatile nature of these chemicals also reduces the potential for dermal exposures from applications of residential pesticide products containing them as inert ingredients.

The conservative E-FAST screening level model was used to estimate the potential for inhalation exposures from the use of residential pesticide products. E-FAST's aerosol paint scenario was selected because it estimates potential acute inhalation exposure over 20 minutes of aerosol paint use in an enclosed utility room. MEK was selected rather than MAK or MIBK because it is has the highest vapor pressure and therefore, has the potential for the highest inhalation exposure. The results of the model run show a peak concentration potential dose (Cp_{pot}) of 299 ppm (884 mg/m^3), which is below the acute inhalation toxicity values for MEK, MAK, and MIBK, and it is well below the doses where developmental toxicity was observed in inhalation studies on MEK, MAK, and MIBK (LOELS are approximately 3,000 ppm, and NOELs are approximately 1,000 ppm). Therefore, no inhalation exposures of concern are anticipated from the use MEK, MAK, and MIBK as inert ingredients in pesticide products.

Considering their low order of toxicity, ready biodegradation in the environment, natural occurrence in a wide variety of foods, and ready metabolism in the body, no dietary or residential risks of concern are identified for MEK, MAK, and MIBK when used as inert ingredients in pesticide products.

Taking into consideration all available information on MAK, MEK, and MIBK, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to MAK, MEK, and MIBK when considering dietary exposure (through food commodities and drinking water) and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the six exemptions from the requirement of a tolerance established for residues of MAK, MEK, and MIBK when used as inert ingredients in pesticide products can be considered reassessed as safe under section 408(q) of the FFDCA.

X. Ecotoxicity and Ecological Risk Characterization

MAK is characterized as having a "low concern level" for fish and aquatic invertebrates in the HPV submission (Geiger, et. al., 1986, and Eastman Kodak, 1998, as cited in HPV, 2002).

The following provides brief overviews of MEK and MIBK from OECD SIDS documents:

"Based on physical and chemical properties, MEK is an unlikely environmental contaminant. It undergoes degradation in the atmosphere and in aqueous environments and has a low degree of toxicity to environmental species." (OECD, 1997)

"MIBK has a low degree of toxicity for aquatic organisms. The lowest reported toxicity threshold for any species is 136 mg/l [8day IC50 (blue algae)]. Toxicity to higher order plants has not been reported." (OECD, 1996)

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APPENDIX A: E-Fast Model Output

The E-FAST model is used by EPA's Office of Pollution, Prevention and Toxics to conduct New Chemicals exposure assessments, and was developed to provide screening-level estimates of the concentrations of chemicals released from consumer products. Modeled estimates of concentrations and doses are designed to reasonably overestimate exposures for use in a screening level assessment. (More information about the model is available at the following website: http://www.epa.gov/opptintr/exposure/docs/efast.htm)

The E-FAST screening level model was used to estimate inhalation exposure potential for MEK-containing aerosol paint products. The average concentration of MEK in products used in the model was 10%. The model's aerosol paint scenario estimates potential inhalation exposure over 20 minutes of aerosol paint use in a utility room. The results of the model run (see CEM Inhalation Exposure Estimates on the following page) show a Peak Concentration Potential Dose (Cp_{pot}) of 884 mg/m^3 (299 ppm). The output from the modeling run is given below:

CEM Inputs		ID Number: Unknown	
Product: Unknown		Chemical Name: MEK aerosol 10%	
Scenario: Aerosol Paint		Population: Adult	
Molecular Weight (g/mole):	72.1	Vapor Pressure (torr):	90.6
Weight Fraction - Median (unitless):	0.01	Weight Fraction - 90% (unitless):	0.01
Inhalation Inputs			
Frequency of Use (events/yr):	6	Years of Use:	11
Mass of Product Used per Event - Median (g):	227	Mass of Product Used per Event -90% (g):	738
Inhalation Rate During Use (m3/hr):	0.55	Duration of Use - Median (hours/event):	0.333
Inhalation Rate After Use (m3/hr):	0.55	Duration of Use - 90% (hours/event):	1
Zone 1 Volume (m3):	20	Whole House Volume (m3):	369
Air Exchange Rate (air exchanges/hr):	0.45	Body Weight (kg):	71.8
Portion of Aerosol in Air (unitless):	0.01		
Activity Patterns			
User: 1 1 1 1 1 1 1 2 3 5 5 4 2 4 6 7 4 2 2 7 4 4 4 1		Start Time: 9	
Non-User: 1 1 1 1 1 1 1 1 3 2 4 4 2 4 7 7 4 2 2 7 4 4 4 1		Room of Use: 5. Utility Room	
Hour: 0 6 12 18			

Note: 75 years = 2.738e+04 days pot - potential dose

Note: The general Agency guidance for assessing short-term, infrequent events (for most chemicals, an exposure of less than 24 hours that occurs no more frequently than monthly) is to treat such events as independent, acute exposures rather than as chronic exposure. Thus, estimates of long-term average exposure like ADD or ADC may not be appropriate for use in assessing risks associated with this type of exposure pattern. (Methods for Exposure-Response Analysis for Acute Inhalation Exposure to Chemicals (External Review Draft). EPA/600/R-98/051. April 1998.

CEM Inhalation Exposure Estimates

ID Number: Unknown

Scenario: Aerosol Paint	Population: Adult
Inhalation Rate (m^3/day): 0.55	Years of Use (years): 11
Body Weight (kg): 71.8	Frequency of Use (events/year): 6

Exposure Units	Result	AT (days)
Chronic Cancer		
$LADD_{pot}$ (mg/kg-day)	6.48e-03	2.74e+04
$LADC_{pot}$ (mg/m^3)	3.53e-02	2.74e+04
Chronic Non-Cancer		
ADD_{pot} (mg/kg-day)	4.42e-02	4.02e+03
ADC_{pot} (mg/m^3)	2.40e-01	4.02e+03
Acute		
ADR_{pot} (mg/kg-day)	8.71e+00	1.00e+00
Cp_{pot} (mg/m^3)	**8.84e+02**	1.00e+00

LADD - Lifetime Average Daily Dose (mg/kg-day) milliequivalents/kg-day.

LADC - Lifetime Average Daily Concentration (mg/m^3)

ADD - Average Daily Dose (mg/kg-day)

ADC - Average Daily Concentration (mg/m^3)

ADR - Acute Dose Rate (mg/kg-day)

Cp - Peak Concentration (mg/m^3)

Cp_{pot} - Peak Concentration Potential Dose