

**METHYL ETHYL KETONE**  
**(CAS No. 78-93-3)**

**VCCEP SUBMISSION**

AMERICAN CHEMISTRY COUNCIL KETONES PANEL

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## GLOSSARY OF TERMS

µg	Microgram
ACGIH	American Conference of Governmental Industrial Hygienists
ADR	Acute Dose Rate
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	Area Under Blood Concentration/Time Curve
BMD	Benchmark Dose
CAA	Clean Air Act
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
CNS	Central Nervous System
CWA	Clean Water Act
EHC	Environmental Health Criteria
EPCRA	Emergency Planning and Community Right to Know Act
HAP	Hazardous Air Pollutant
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
kg	Kilogram
MEK	Methyl Ethyl Ketone
mg	Milligram
MRL	Minimal Risk Level
MSDS	Material Safety Data Sheet
NCEA	National Center for Environmental Assessment
NED	No Effect Dose
NHANES	National Health and Nutrition Examination Survey
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
OECD	Organization of Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration
ppb	Parts Per Billion
ppm	Parts Per Million
RCRA	Resource Conservation and Recovery Act
RfC	Inhalation Reference Concentration
RfD	Oral Reference Dose
sBA	Secondary-butyl alcohol or 2-butanol or sec-butanol
SIAR	Screening Information Assessment Report
SIDS	Screening Information Data Set
STEL	Short-Term Exposure Limit
TLV	Threshold Limit Value
TSCA	Toxic Substances Control Act
TWA	Time-Weighted Average
VOC	Volatile Organic Compound
VCCEP	Voluntary Children's Chemical Evaluation Program
WHO	World Health Organization

## 1. Executive Summary

### Introduction

The sponsors of methyl ethyl ketone (MEK) have compiled the information in this submission to meet the requirements of the Voluntary Children's Chemical Evaluation Program (VCCEP). Consistent with the Pilot Program announcement,<sup>1</sup> this submission includes a hazard assessment, exposure assessment, risk assessment, and data needs assessment. Background information also is provided concerning the current regulatory status of MEK, recent agency assessments, compilations of relevant peer-reviewed hazard information, and other topics of interest. The biomonitoring data and indoor air monitoring data that provided the basis for including MEK in the Program also are discussed in the context of relevant health effects information.

MEK is generally recognized to have low acute and chronic toxicity. EPA recently updated the IRIS database entry for MEK, which now includes an inhalation reference concentration (RfC) of 5.0 mg/m<sup>3</sup>, and an oral reference dose (RfD) of 0.6 mg/kg/day. The RfC and RfD values, as a matter of EPA policy, are intended to represent exposures that may be continued for a lifetime for the general population, including sensitive subgroups, without appreciable risk of adverse effects. The relatively high values for MEK reflect its low systemic toxicity. Reasonably anticipated children's exposures are below these levels.

The Executive Summary provides an overview of the information presented in each section of the submission. Citations generally are not provided in the Executive Summary, but are found in the main text.

### Basis for VCCEP Listing

MEK was selected for the VCCEP Pilot Program for three reasons: (1) hazard data at least equal to Tier 1 of the VCCEP Pilot are available from an OECD SIDS Screening Information Assessment Report (SIAR); (2) MEK has been reported in human blood in the NHANES study; and (3) MEK has been detected in indoor air. Available toxicity data for MEK in fact exceed the Tier I VCCEP requirements, and has been found sufficient by EPA for derivation of chronic exposure levels (inhalation and oral) that are deemed to be without appreciable risk to the general population (including potentially sensitive subgroups) assuming continuous exposure for a lifetime. MEK blood level data were reported in NHANES because the reported blood levels are consistent with MEK's natural presence at measurable levels in a wide variety of foods, including meats, vegetables, fruits, nuts and dairy products. Further, the reported blood levels in NHANES are below what one would predict from inhalation exposures at the IRIS RfC of 5 mg/m<sup>3</sup>. The indoor air data also are unremarkable; MEK has been found in indoor air at levels that are approximately 1000-fold below the inhalation RfC – levels that clearly cannot be expected to pose any significant health concerns.

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<sup>1</sup> 65 Federal Register 81700 (December 26, 2000).

## **Recent Regulatory Assessments and Other Peer-Reviewed Assessments**

MEK has been reviewed in several recent assessments by regulatory agencies or in peer-reviewed publications. These assessments include:

**IRIS Assessment (2003).** EPA's National Center for Environmental Assessment (NCEA) recently posted an updated IRIS summary and Toxicological Review for MEK on its website. The documents include an oral RfD of 0.6 mg/kg/day and an inhalation RfC of 5.0 mg/m<sup>3</sup>.

**EPA EPCRA Review (1998).** EPA reviewed the available toxicity data for MEK in 1998, when considering a petition to remove MEK from the list of "toxic chemicals" maintained under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA). EPA concluded as follows:

- "Available data indicate that MEK has low acute toxicity."
- "Available data indicate that MEK has low chronic toxicity."
- "[T]he concern for developmental toxicity appears to be low."
- "[T]he concern for reproductive toxicity appears to be low."
- "[S]everal well-designed repeated-dose oral and inhalation studies in laboratory animals demonstrate low systemic toxicity with MEK."
- "[T]here is no convincing experimental evidence that MEK is neurotoxic."
- "The hazard assessment strongly indicates that . . . MEK has low acute and chronic (systemic) toxicity in that effects occur only at high doses."<sup>2</sup>

The petition was denied based on MEK's status as a volatile organic compound, or VOC. VOCs contribute to the formation of ozone, which is the primary component of smog.

**EPA CAA Review (2003).** In 1996, the American Chemistry Council (ACC) Ketones Panel submitted a petition to EPA requesting that the Agency remove MEK from the list of hazardous air pollutants (HAPs) under Section 112 of the Clean Air Act. On May 30, 2003, EPA issued a proposal to delist MEK as a HAP.<sup>3</sup> The proposal is "based on the results of a risk assessment demonstrating that emissions of MEK may not reasonably be anticipated to result in adverse human health or environmental effects."

**OECD SIDS Dossier and SIAR (SIAM 6, 1997).** The SIDS Screening Information Assessment Report (SIAR) for MEK provides a comprehensive summary of relevant hazard information and based on that hazard assessment concludes that MEK has "a low order of toxicity" and is "a low priority for further work." The United States was the sponsoring country and EPA and OECD scientists reviewed and approved the SIAR. Secondary-butyl alcohol (sBA or 2-butanol), the direct metabolic precursor for MEK and a known metabolite of MEK, recently was reviewed in the OECD SIDS process (SIAM 14; March 2002) with its own SIDS Dossier, SIAR, and package

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<sup>2</sup> 63 Fed. Reg. 15195, 15197-99 (March 30, 1998).

<sup>3</sup> 68 Fed. Reg. 32606.

of Robust Summaries. The United States was the sponsor country for sBA and, as such, reviewed and commented on all support documentation. Like MEK, the sBA producers sponsored sBA on a voluntary basis, and the review resulted in a consensus judgment by scientists from the participating countries that further testing and evaluation is a low priority because of the low hazard profile of this precursor to MEK. (The OECD SIARs do not include an extensive assessment of potential children's exposures, as contemplated by the VCCEP pilot program.)

***Patty's Toxicology (Fifth Edition, Volume 6, Morgott, Topping & O'Donoghue, pp. 117-156, 2001).*** The Ketones of Four or Five Carbons Chapter in *Patty's Toxicology* provides an extensive discussion of the relevant scientific literature on MEK's potential health effects. The text consists of 39 pages and includes over 300 references. Information pertaining to metabolism and toxicokinetics is presented, along with discussion of animal and human data pertaining to the various toxicity endpoints of concern to the VCCEP.

**World Health Organization Environmental Health Criteria Document (1992).** The WHO International Programme on Chemical Safety (IPCS) published an Environmental Health Criteria (EHC) document for MEK in 1992. The initial draft was prepared by Dr. R. B. Williams of the U.S. EPA Office of Research and Development, who served as one of two co-rapporteurs. The EHC document concludes: "MEK on its own appears a relatively safe organic solvent . . ." (p. 12).

**ATSDR Toxicological Profile (1992).** The Agency for Toxic Substances and Disease Registry toxicological profile of MEK also provides an extensive discussion of available hazard and exposure information. The document does not include calculation of "minimal risk levels" (MRLs), but does conclude that exposure to MEK "appears relatively innocuous." (p. 35).

### **Production, Use and Releases to the Environment**

MEK is manufactured in enclosed, continuous processes. Estimated total global capacity in 1999 was approximately 1,065 thousand metric tons; United States production amounted to 260,000 metric tons.

MEK is used in surface coatings (55%), adhesives (12%), printing inks (4%), chemical intermediates (6%), magnetic tapes (5%) and lube oil dewaxing agents (6%). MEK also is used as an extraction medium for fats, oils, waxes and resins.

EPA's EPCRA Toxics Release Inventory (TRI) database indicates total reported releases of MEK to air, water and land in 2001 were 29,094,942; 47,718 and 124,263 pounds, respectively. Extensive air dispersion modeling conducted in connection with the ACC petition to remove MEK from the Clean Air Act list of hazardous air pollutants shows that airborne concentrations beyond facility boundaries are well below the EPA inhalation RfC, such that no adverse health effects should be expected, even for sensitive subgroups exposed continuously for a lifetime.

### **Hazard Assessment**

In the progressive and methodical development of the MEK hazard assessment database, most toxicity tests listed in Tier 1, Tier 2, and Tier 3 of the Pilot Announcement have been conducted for MEK (see Section 7) and/or sec-butanol (sBA - a direct metabolic precursor for MEK; see Section 7.3), or have previously been determined to be scientifically unnecessary (see Section 10.1). In some cases, multiple studies are available to support an assessment of the testing

endpoint identified. The key studies are briefly addressed below; highlighted in Table 7.1; presented in Section 7; and their robust summaries are provided in Appendix B.

#### Tier 1 Studies:

- **Acute Toxicity (Oral):** MEK has a low order of toxicity following single oral exposure in rodents. The LD<sub>50</sub> in adult rats is 6.86 mg/kg (5.59 - 8.45 range).
- **In vitro Gene Mutation:** MEK is not mutagenic in the Ames bacterial mutagenesis assay and did not induce mitotic gene conversion in yeast.
- **Repeated Dose Toxicity & Reproductive Toxicity (1-Generation):** Superseded by Tier 2 90-Day Subchronic Toxicity and 2-Generation Reproductive Toxicity studies identified below.
- **In vitro Chromosomal Aberrations:** MEK did not induce chromosome damage *in vitro* in RL<sub>4</sub> mammalian cells.

#### Tier 2 Studies:

- **90-Day (Subchronic) Toxicity in Rodents:** MEK produced no observable toxic effects at doses up to 5000 ppm in a 90-Day inhalation toxicity study. Histopathological studies included extensive examination of reproductive organs. None of the examined tissues (testes, epididymides, seminal vesicles, vagina, cervix, uterus, oviducts, and ovaries) showed lesions attributed to MEK exposure.

MEK failed to show any significant clinical or histopathological evidence of neurological dysfunction at 500 ppm (22 hr/day) in a 6-Month repeated dose inhalation study.

- **Prenatal Developmental Toxicity (two species) & Reproductive Toxicity:** MEK was not teratogenic in 2 rat and 1 mouse Prenatal Developmental Toxicity studies (pup NOAELs/NOEL ranged from 1000 - 3500 ppm) or in a rat sBA Prenatal Developmental Toxicity study where the pup NOEL was 1771 mg/kg/day (dosed through total gestation period).

sBA (direct metabolic precursor for MEK) was not considered a reproductive hazard in a 2-Generation Reproductive Toxicity study in rats. The maternal and pup NOAELs were 1771 mg/kg/day.

- **In vivo Mammalian Bone Marrow Erythrocyte Micronucleus Cytogenetic Toxicity:** MEK did not induce an increased number of micronucleated polychromatic erythrocytes in CD-1 mice in a Bone Marrow Erythrocyte Micronucleus Assay.
- **Immunotoxicity:** MEK exposure to vapors at 5000 ppm for 6 hr/day, 5 days/week in a subchronic study showed no indication that immune enhancement or immune suppression takes place. White blood cell counts/differentials, gross and histopathological examinations of immune system tissues (lymph nodes and spleen) were performed as part of repeated-dose studies. Likewise, in the sBA 2-Generation Reproductive Toxicity study at a dosage of 1771 mg/kg/day there were no indications of immune system modulation.

Acetone (methyl methyl ketone, a structurally similar compound to MEK) was evaluated in a 28-day immunotoxicity study in CD-1 mice. Time-weighted average dosages based on water consumption and actual body weights ranged from 121 to 1144 mg/kg/day. The acetone treatment did not produce any alterations in lymphoid organ weights (spleen or thymus) that were statistically different from controls and no effects were noted for spleen cellularity. The mouse Antibody-Plaques Forming Cell (AFC) assay response to sheep red blood cells (SRBCs) following the acetone treatment challenge was evaluated on study day 29. The AFC assay responses ranged from 1088 – 1401 AFC/10<sup>6</sup> splenocytes following water or acetone administration, and were not statistically different from control values. Acetone (methyl methyl ketone) did not produce immunotoxicity in CD-1 mice, and no treatment-related effect of acetone on the SRBC antibody response was observed.

MEK was not a contact allergen in the mouse ear-swelling test, and there was no evidence of MEK-induced skin sensitization of Hartley albino guinea pigs in a study where MEK was used as the vehicle control/solvent.

MEK produced no sensitization reactions in human volunteers exposed to a 20% MEK in petrolatum mixture, and no irritation was seen following a 48-hour closed-patch test in humans.

- **Metabolism and Pharmacokinetics:** MEK pharmacokinetics and metabolism are interrelated with sBA and toxicology data sets indicate that each is a good surrogate for the other. MEK absorption is rapid via dermal contact, inhalation, ingestion and intraperitoneal injection. It is rapidly transferred into the blood and on to other tissues. The solubility of MEK appears similar for all tissues. The clearance of MEK and its metabolites in mammals is essentially complete in 24 hours. MEK is metabolized in the liver, where it is primarily oxidized to 3-hydroxy-2-butanone and subsequently reduced to 2,3-butanediol. A small portion may be reduced to 2-butanol, but 2-butanol is rapidly oxidized back to MEK. The bulk of MEK taken into the mammalian body enters the general metabolism and/or is eliminated as simple compounds such as carbon dioxide and water.

### Tier 3 Studies:

- **Carcinogenicity or Combined Chronic Toxicity/Carcinogenicity:** MEK is not considered potentially carcinogenic given lack of genotoxic potential and low order of repeated dose toxicity. MEK produced minimal or no systemic effects in laboratory animals following repeated exposures to high doses (5000 ppm, 6 hr/day, 5 days/week for 90 days or 500 ppm MEK vapor for 22 hr/day for up to 6 months). Based on the metabolism of MEK and sBA, rapid absorption, metabolism and/or excretion as conjugates, similar expressions of toxicity as seen in animals are expected in humans. As EPA has concluded, “MEK is unlikely to be carcinogenic based on the lack of any structural features or alerts indicative of carcinogenic potential as a result of mechanism-based structure-activity relationship (SAR) analysis (Woo *et al.* 2002). Further, Woo has given MEK a low concern rating (unlikely to be of cancer concern) based on comparison to acetone for which there is no evidence of carcinogenicity, and the fact that there is no evidence that unsubstituted mono-ketones have been associated with carcinogenicity/genotoxicity.” 68 Fed. Reg. 32606, 32613 (May 30, 2003). The same conclusion is reached in the recent IRIS Toxicological Review of Methyl Ethyl Ketone (2003) (pp. 48-49 and 56) and IRIS Summary (p. 16).
- **Neurotoxicity Screening Battery:** MEK was excluded from the TSCA neurotoxicity endpoint test rule based on EPA’s conclusion that the neurotoxicity data for MEK were

“adequate.” Moreover, given the lack of observed clinical neurotoxicity symptoms and lack of neuropathology in rats exposed for 3-6 months, MEK is not considered neurotoxic. Extensive neuropathology was performed on the 90-day and 6-month repeated-dose animals that were also clinically asymptomatic. In the 90-day study a subset of 5 males and 5 females, exposed to 0, 1250, 2500, or 5000 ppm MEK vapor for 6 hr/day, 5 days/week, were dedicated for special neuropathology. The neuropathological studies included specimens of the sciatic and tibial nerves and medulla that were evaluated by the “teased fiber” method. The study results failed to show any significant clinical or histopathological evidence of neurological dysfunction. In the 6-months inhalation study (22 hr/day to 500 ppm MEK vapor), tissues were sampled from regions of maximum vulnerability determined in previous experimental studies of hydrocarbon neuropathy and included cerebellar vermis, cervicomedullary junction, lumbar cord, dorsal and ventral spinal roots, and spinal ganglia, sciatic notch, and three levels of tibial nerve. The tibial nerves were subjected to the “teased” single fiber technique of evaluation. This study with extensive neuropathologic investigation did not reveal any lesions that could be attributed to MEK exposure. The IRIS Toxicological Review of Methyl Ethyl Ketone (2003) concludes, “Several well-conducted studies in experimental animals...provide no convincing evidence that repeated exposure to MEK, by itself, is capable of producing persistent neurological effects.” (p. 54). Similarly, the IRIS summary states, “Animal studies provide no convincing evidence that exposure to MEK alone causes persistent neurotoxic effects.” (p. 13).

- **Developmental Neurotoxicity:** Developmental neurotoxicity has been indirectly evaluated via the tissue examination of fetuses in multiple guideline-quality developmental toxicity studies (3 MEK and 2 sBA) and evaluation of the newborn pups in the 2-generation reproduction developmental toxicity study (sBA). The results showed no indication of a primary effect on the nervous system. Clinical / behavioral observations in long-term (3-6 months) rodent studies and human exposure studies showed no concern for neurotoxicity. Extensive neuropathology was performed on the 90-Day and 6-Month Repeated-dose animals that were also clinically asymptomatic.
- **Human Behavioral Performance Tests:** MEK exposures at 200 ppm for 4 hours produced no significant neurological effects in any of the three human behavioral performance tests on a total of 189 subjects.

### **Exposure Assessment**

Information on all known sources (natural and anthropogenic) of MEK, media concentrations, and physical-chemical properties were gathered and summarized. All pathways potentially relevant to children’s exposure were considered, including child contact with environmental media (indoor and outdoor air, surface water, soil), food, drinking water, potential for parental transfer to child (breast milk or dermal contact), direct consumer product use or presence during consumer product use, and other sources. A tiered approach to exposure assessment was used, based upon screening level, conservative techniques with refinement, as indicated. Pathways considered included:

#### Ambient Media:

Outdoor Air - typical and source dominated areas

Indoor Air - typical or indoor sources - residential, school and car

Soil

Food - natural occurrence

Breast Milk - background and from occupationally-exposed mother

## Water

### Specific Sources:

Consumer Product Use (inhalation and dermal)

Food-Flavoring, food industry use

Other Sources (building materials, pharmaceuticals)

MEK is a naturally occurring human metabolite, is present naturally in foods across all food groups, and is produced by microbes, algae, plants and other organisms. It is also released to the environment via anthropogenic production, where it primarily partitions to air. Its primary use is industrial, but it can also be found in consumer products, especially coatings and adhesives, and has minor use in the food industry as an extraction agent and flavoring agent.

Results indicate that on a chronic basis, natural occurrence in food is likely the main exposure pathway in the general population of children. Ambient media concentrations are generally below detection limits or low, even in source dominated areas. Indoor uses of consumer products can result in higher acute exposures, but these are short-lived. MEK is rapidly metabolized and excreted (thus acute exposures do not lead to any increase in body burden over time).

Based upon physical-chemical properties, use information, and/or monitoring data, some pathways were found to result in low or negligible exposures (ambient air, water, soil, pipe cement and primer, pharmaceuticals, and food industry use). The only exposure pathway identified unique to children was breast milk. None of the consumer products that contain MEK are targeted specifically towards young children, with the exception of hobby model paints and adhesives that are targeted towards older children and adults. Integrated data from consumer product databases, Material Safety Data Sheets (MSDSs), and store visits were used to identify the consumer products with the greatest exposure potentials, for further evaluation. The following consumer products were quantitatively evaluated for both inhalation exposures (active use for older children only and passive presence during use for all ages) and dermal exposures when appropriate (active use for older children only):

- Carburetor cleaner (aerosol)
- Spray Paint
- Wood stain/ varnish (aerosol)
- Paint thinner (liquid) -use as an addition to wood varnish, use as a brush cleaner, use in clean-up (dermal - teenage active use only)
- Adhesives (household, liquid) - hobby use (inhalation, for dermal- teenage active use only), household use
- Hobby model paints (liquid)

Child exposure was estimated for all plausible pathways, for <1, 1-2, 3-5, 6-11, 12-15 and 16-19 year age groups using conservative assumptions intended to overestimate, rather than underestimate, exposure. The range of exposures predicted for individual consumer products (across all age groups, passive and active scenarios) are:

- 4 hr TWA: 0.03 - 92 mg/m<sup>3</sup>
- Day of use dose: 0.0002 - 1.62 mg/kg/day

- Chronic dose: 0.00002 - 0.016 mg/kg/day (based upon median use exposure estimates, 90th percentile frequency of use each year, all use indoors, and MEK in product for every use)

### **Risk Assessment**

Risk assessment involves the integration of hazard information and exposure assessment results to provide qualitative and quantitative estimates of risk. Exposure estimates have been derived for a wide variety of potential sources – natural and man made. The risk assessment focuses on potential exposures to children from man-made sources. Chronic exposures are compared to EPA's inhalation reference concentration (RfC) of 5.0 mg/ m<sup>3</sup>, and the oral reference dose (RfD) of 0.6 mg/kg/day, which, as already stated, are intended to represent exposures that may be continued for a lifetime without appreciable health risks. These comparisons support the following conclusions:

- **Ambient and Indoor Air.** Exposures from outdoor and indoor air are well below the RfC, and thus are deemed to show no appreciable health concern.
- **Water and Soil.** MEK generally has not been detected in water or soil, and potential exposures to children were determined to be insignificant.
- **Facility Releases.** EPA's Air Office recently conducted an extensive assessment of potential exposures from facilities and concluded that likely exposures are well below the RfC, such that they may not reasonably be expected to pose any appreciable health risks.
- **Occupationally-Exposed Parents.** Potential exposure via breast milk was estimated using conservative assumptions that are not considered realistic. Even so, estimated exposure is below the RfD, indicating there should be no appreciable health risk. Exposure via contaminated clothing or skin is deemed unlikely to be significant because of MEK's relatively high vapor pressure and ready evaporation.
- **Consumer Products – Repeated Use.** Numerous consumer product uses were assessed using conservative assumptions. In all cases, potential chronic exposures, expressed in mg/kg/day, are estimated to be below the RfD for all age groups, usually by a very large margin. Margins of safety, determined by dividing the RfD by the potential chronic exposure, range from 37.5 to >20,000 for the various consumer product scenarios that have been assessed (since the RfD is intended to represent an exposure that may be continued daily for a lifetime without appreciable health risks, any MOS > 1 should be deemed adequate). Use of these products therefore is not expected to pose any chronic health hazards.
- **Consumer Products – Day of Use.** The principal concern for short-term exposures to MEK pertains to its potential to cause sensory irritation. Human studies conducted by NIOSH establish a NOAEL of 590 mg/m<sup>3</sup> (200 ppm) for sensory irritation, based on exposures up to 4 hours. Four-hour time-weighted average (TWA) inhalation exposures have been calculated for each consumer product use scenario, and in each case the value is well below 590 mg/m<sup>3</sup>, indicating a low potential for acute effects. Some product use scenarios are

assumed to last less than 4 hours, but in these cases task-time-weighted average exposures are still below 590 mg/m<sup>3</sup>. MEK has a strong odor at 200 ppm, and that odor combined with explicit product warnings to use MEK-containing products with ample ventilation should reduce opportunities for sensory irritation from excessive acute exposures. However, if a consumer product containing MEK is not used as intended or in a manner consistent with label warnings, then effects described on most product labels (e.g., headache, nausea) or other symptoms or sensory irritation may occur, depending on the circumstances of improper use.

- **Potential for Aggregate Exposures.** Chronic exposures were estimated for selected consumer product use scenarios believed to represent the highest potential for exposure, as opposed to all consumer product use scenarios (an infeasible task). Potential aggregate chronic exposures for all modeled consumer product use scenarios for all age groups are well below the RfD. The potential for aggregate chronic exposures from non-modeled sources to pose significant health risks is considered remote. Key points include:
  - MEK is eliminated from the body very quickly.
  - Exposures from sources that children are expected to encounter on a daily basis (e.g., indoor and outdoor air, sources of drinking water, food) are very low, and in particular well below the RfC and RfD.
  - Exposures from representative consumer products – products that are believed to represent the high end of potential exposures – are quite low by comparison to the RfD. Even using conservative assumptions, estimated chronic exposures in most cases are less than 1 percent of the RfD.
  - Most products that have been identified as containing MEK are not intended for use by children, such that children’s exposure typically would occur, if at all, through the child’s presence in the room where the product is used or somewhere else in the home.
  - Most products that have been identified as containing MEK also typically are used only on an intermittent basis and not by all persons. Since product use information indicated that periods of greater than a year could elapse between uses, the estimated chronic exposure values assumed a 90<sup>th</sup> percentile use frequency for each and every year.
  - Analysis of consumer products indicated that MEK is typically present in only a fraction of available brands for a given type of product. Chronic exposure values were estimated assuming MEK was present in 100% of the brands for each product.

Based on the foregoing points, there is no reason to anticipate that use of multiple products would cause children’s exposures to exceed the RfC or RfD. There does not appear to be a reasonable basis for concern that multiple sources of MEK exposures might in the aggregate pose significant health risks to children.

## **Data Needs Assessment**

### **Hazard Information**

Most of the Tier 1, Tier 2 and Tier 3 studies included in the VCCEP program have been conducted for MEK or sBA. The exceptions are guideline studies for immunotoxicity, developmental neurotoxicity and chronic toxicity/oncogenicity. For reasons presented in Section 7 (Hazard Assessment) and Section 10 (Data Needs Assessment), the VCCEP sponsors believe available data are not indicative of likely hazards in these areas, such that further testing is scientifically unnecessary. This conclusion is consistent with the OECD SIDS assessment and EPA's prior assessment under TSCA (when chronic testing was deemed not necessary). Further, the existing data have been found sufficient for the derivation of an inhalation RfC and oral RfD, and the exposure assessment demonstrates that reasonably anticipated exposures are below these health benchmarks. In summary, existing studies demonstrate that MEK has low acute and systemic toxicity, and there would appear to be no scientific justification for conducting additional toxicology studies of MEK.

### **Exposure Information**

For a compound like MEK, additional exposure assessment work is always possible. The VCCEP sponsors believe, however, that the information presented in this document is adequate to demonstrate that reasonably anticipated exposures to MEK are not likely to exceed relevant health benchmarks and are not likely to present significant health risks to children. The exposure analyses were performed using conservative assumptions, assuming maximum MEK concentrations in products, and evaluating products with the greatest exposure potential. Accordingly, the VCCEP sponsors believe additional exposure assessment work also should be a low priority, and is not necessary to meet the objectives of the VCCEP program.

## 2. Basis for Inclusion of MEK in VCCEP Pilot Program

### 2.1 Introduction

In selecting compounds for the VCCEP Pilot Program, EPA relied on biomonitoring and environmental monitoring databases that it considered relevant to assessing the potential for children's exposure.<sup>4</sup> Availability of hazard data was an additional factor that influenced chemical selection decisions; EPA stated that it wanted to select chemicals for which Tier I hazard data were available. MEK was selected for three reasons: (1) an OECD SIDS Screening Information Assessment Report (SIAR) is available; (2) MEK has been reported in human blood in the NHANES study; and (3) MEK has been detected in indoor air.<sup>5</sup> As described later in this document, the available toxicity data for MEK exceeds Tier I VCCEP requirements, and has been found by EPA sufficient to support derivation of a chronic inhalation reference concentration (RfC) and a chronic oral reference dose (RfD), both of which reflect MEK's low toxicity. The availability of extensive hazard information is an advantage for MEK in the Pilot Program. The blood level data and indoor air monitoring data show no appreciable health concern and should not be viewed as indicating a need for any testing or risk management actions.

### 2.2 NHANES Data

MEK was found in the blood of subjects in the NHANES study<sup>6</sup> in greater than 75 percent of test samples at a median concentration of 5.4 ppb.<sup>7</sup> However, these blood levels, which are believed to reflect primarily dietary exposures, are not a basis for concern. As already noted, EPA's recently updated IRIS database for MEK includes safe levels for continuous oral and inhalation exposure to MEK for a lifetime, including sensitive subgroups. It is possible, using conservative assumptions, to calculate blood levels that might be expected in humans exposed to MEK at the updated inhalation RfC of 5.0 mg/m<sup>3</sup>. This calculation is presented in Appendix E to this document, and shows that exposures to MEK at the updated RfC should be expected to result in blood levels well above the median value reported in NHANES. In other words, the median value reported in NHANES is below levels EPA found to be without appreciable risks of adverse effects.

It also is important to recognize that MEK is emitted to the atmosphere from such natural sources as European firs, junipers, cedars, cypress trees and ferns, and has been identified as a natural component of numerous foods, including roasted barley, cheddar cheese, bread, honey, chicken, roasted nuts, oranges, nectarines, black tea and rum. 2-Butanol (metabolic precursor of MEK) also occurs naturally in many foods, including meats, vegetables, fruit juices and dairy products. (The natural presence of MEK and 2-butanol in the environment and in a normal, healthy diet is described further in Sections 6 and 8.) Thus, the general population is exposed to MEK from natural sources on an almost continuous basis, such that low levels in blood should be expected. Further, MEK is a human metabolic byproduct (Scriver *et al.* 2001).

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<sup>4</sup> See VCCEP Federal Register Notice (Dec. 26, 2000), at III.Q.

<sup>5</sup> See Pilot Announcement, Table 1.

<sup>6</sup> NHANES (National Health and Nutrition Examination Survey) was conducted from 1988 through 1994 and included blood levels of 32 VOCs in a sample of approximately 800 volunteers.

<sup>7</sup> Pilot Announcement at 81705, Table 2.

EPA considered the biomonitoring data as providing a strong rationale for identifying a chemical for the VCCEP Pilot Program.<sup>8</sup> In the case of MEK, however, the reported blood levels likely reflect MEK's natural presence in the diet, and are below levels that might pose a concern.

### 2.3 Indoor Air Monitoring Data

In one of the two studies cited by EPA, four data points were reported with measurable concentrations of MEK in indoor air; the average concentration was 9.2 ppb, and the median was 7.2 ppb (Shah and Singh 1988). These values are almost three orders of magnitude below the RfC of 5.0 mg/m<sup>3</sup> (approximately 1.7 ppm). The other study reported a 90<sup>th</sup> percentile concentration of 16 µg/m<sup>3</sup> MEK and a 98<sup>th</sup> percentile concentration of 38 µg/m<sup>3</sup> – values that also are close to three orders of magnitude lower than the RfC (Brown *et al.* 1994). On this basis, one can conclude that indoor air levels of MEK do not present a health concern. The MEK VCCEP sponsors are not aware of any data that would suggest that the reported indoor air levels of MEK present a health concern. Further, low indoor air MEK concentrations were reported in additional indoor air studies summarized in Appendix G.4 and discussed in Section 8.

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In summary, the available biomonitoring data and environmental monitoring data for MEK are not indicative of significant human exposures and do not provide a basis for concern for children's health. The extensive hazard information that is available for MEK, however, and the availability of chronic health values for inhalation and oral exposures, do facilitate evaluation of MEK in the Pilot Program.

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<sup>8</sup> See VCCEP Pilot Announcement, Section III.B.

### 3. Previous Assessments

MEK has been the subject of several recent assessments by government agencies and in peer-reviewed publications. While none focused exclusively on children, they nonetheless are relevant. This section provides a brief overview of some of the more comprehensive reviews, and provides electronic links where available.

#### 3.1 IRIS Assessment

EPA's National Center for Environmental Assessment (NCEA) recently updated the Integrated Risk Information System (IRIS) database entry for MEK. The IRIS summary (23 pages) and Toxicological Review (99 pages plus appendices) were posted on EPA's website on September 26 2003, and may be found at [www.epa.gov/iris](http://www.epa.gov/iris). The documents include an oral reference dose (RfD) of 0.6 mg/kg/day based on a 2-generation reproduction study of 2-butanol (metabolic parent of MEK). EPA calculated several benchmark dose levels associated with decreased pup body weight, and identified the lowest (657 mg/kg/day) as its point of departure. The Agency applied total uncertainty factors of 1000 (10 for interspecies extrapolation, 10 to protect sensitive subpopulations, and 10 for database deficiencies) to derive the RfD.

The RfC is 5.0 mg/m<sup>3</sup>, and is based on two MEK developmental toxicity studies (Deacon *et al.* 1981; Schwetz *et al.* 1991 (also known as Mast 1989)). EPA calculated benchmark dose levels for extra ribs in rats; decreased fetal body weight in mice; and misaligned sternebrae in mice. The lowest value, 5202 mg/m<sup>3</sup> for misaligned sternebrae in mice, was chosen as the point of departure. Although the IRIS documentation notes that peak exposure ( $C_{max}$ ) may be a more relevant exposure metric than area under the curve (AUC) for short half-life compounds such as MEK, EPA nonetheless makes the conservative assumption that AUC is the relevant exposure metric, and adjusts the lowest benchmark dose to account for continuous exposure, resulting in a  $LEC_{(HEC)}$  of 1517 mg/m<sup>3</sup>. EPA applied total uncertainty factors of 300 (3 for interspecies extrapolation, 10 for sensitive individuals and 10 for incomplete database) to derive the RfC of 5.0 mg/m<sup>3</sup>, which represents a "continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious noncancer health effects during a lifetime."<sup>9</sup>

As explained later in the text (Section 7.13 – Selection of Health Benchmarks), IRIS RfD and RfC values are by design intended to be conservative (health protective). NCEA initially proposed an oral RfD of 0.7 mg/kg/day and an inhalation RfC of 15.0 mg/m<sup>3</sup>.

As described below, EPA has expressly recognized that MEK is unlikely to pose a reproductive or developmental toxicity hazard. Use of the above-described RfC (5.0 mg/m<sup>3</sup>) and RfD (0.6 mg/kg/day) values does not contradict these previous assessments. See related discussions in Section 7.6 (Reproductive Toxicity) and Section 7.7 (Developmental Toxicity and Teratogenicity).

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<sup>9</sup> EPA (1994). *Methods for the Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*, p.1-3 (EPA/600/8-90/066F).

### 3.2 EPA EPCRA Review

EPA conducted a comprehensive review of the data on the potential health effects of MEK in 1998, when considering whether to grant a petition to remove MEK from a list of toxic chemicals maintained under Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA).<sup>10</sup> EPA reached the following conclusions:

- “[T]he concern for developmental toxicity appears to be low.”<sup>11</sup>
- “[T]he concern for reproductive toxicity appears to be low.”<sup>12</sup>
- “Available data indicate that MEK has low acute toxicity.”<sup>13</sup>
- “Available data indicate that MEK has low chronic toxicity.”<sup>14</sup>
- “[S]everal well-designed repeated dose oral and inhalation studies in laboratory animals demonstrate low systemic toxicity with MEK.”<sup>15</sup>
- “[A]t present, there is no convincing experimental evidence that MEK is neurotoxic....”<sup>16</sup>
- “The hazard assessment strongly indicates that . . . MEK has low acute and chronic (systemic) toxicity in that effects occur only at high doses.”<sup>17</sup>

EPA denied the petition solely because MEK is a volatile organic compound (VOC), and VOCs contribute to the formation of ozone, the primary component of smog. As indicated above, the Agency expressly found that MEK itself did not pose significant toxicity concerns.

### 3.3 EPA Clean Air Act Review

In 1996, the ACC Ketones Panel submitted a petition to EPA requesting that the Agency remove MEK from the list of HAPs under Section 112 of the Clean Air Act. The Panel’s petition (and subsequent supplemental documentation) included detailed hazard and exposure information on MEK, and demonstrated that MEK met the statutory criteria for delisting.

On May 30, 2003, EPA issued a proposal to delist MEK as a HAP.<sup>18</sup> In evaluating MEK, the Agency reached the following conclusions:

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<sup>10</sup> 63 *Fed. Reg.* 15195 (March 30, 1998).

<sup>11</sup> *Id.*

<sup>12</sup> *Id.*

<sup>13</sup> *Id.* at 15197.

<sup>14</sup> *Id.*

<sup>15</sup> *Id.*

<sup>16</sup> *Id.* at 15197-15198 (quoting IRIS database).

<sup>17</sup> *Id.* at 15199.

- “Methyl ethyl ketone has been tested for activity in an extensive spectrum of *in vitro* and *in vivo* genotoxicity assays and has shown no evidence of genotoxicity in most assays. . . . Overall, studies of MEK yield little or no evidence of genotoxicity.”<sup>19</sup>
- “MEK may not reasonably be anticipated to be carcinogenic.”<sup>20</sup>
- “The available data indicate that MEK is not likely to be a reproductive toxicant.”<sup>21</sup>
- “[T]here is no convincing experimental evidence that MEK is neurotoxic . . . other than possibly inducing CNS (central nervous system) depress[ion] at high exposure levels.”<sup>22</sup>

EPA used a “prospective” RfC of 9.0 mg/m<sup>3</sup> for its assessment. Based on an exposure assessment submitted by petitioners using EPA-approved methodologies, EPA concluded that the maximally exposed individual from facility releases would have annual exposures only one-tenth the prospective RfC of 9.0 mg/m<sup>3</sup>, while concentrations near MEK emission sources in most cases would be two to ten-fold lower than that (*i.e.*, 20 to 100 times lower than the prospective RfC of 9.0 mg/m<sup>3</sup>).<sup>23</sup> EPA further concluded that, because the Panel’s petition used conservatively modeled ambient concentrations as a surrogate for exposure, “[b]ased upon the likely proximity of inhabitable areas and knowledge of human activity patterns, we believe that actual exposures will be far less than predicted exposures that were derived from the dispersion analysis.”<sup>24</sup>

In publishing the proposed delisting of MEK, the Agency concluded:

“[T]he assessment applies conservative assumptions to bias potential error toward protecting human and ecological health. Thus, EPA is confident that even when we consider the uncertainties in the petition’s initial assessment and in the additional analyses, the results are more likely to over-estimate than under-estimate true exposures and risks. Based on our evaluation of the petition and subsequent analyses, we judge that the potential for adverse human health and environmental effects to occur from projected exposures is sufficiently low to provide reasonable assurance that such adverse effects will not occur. . . . As described above, EPA’s proposed decision to delist MEK is based on the results of a risk assessment demonstrating that

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<sup>18</sup> 68 Fed. Reg. 32606.

<sup>19</sup> *Id.* at 32613.

<sup>20</sup> *Id.*

<sup>21</sup> *Id.*

<sup>22</sup> *Id.*

<sup>23</sup> *Id.* at 32616.

<sup>24</sup> *Id.* at 32619.

emissions of MEK may not reasonably be anticipated to result in adverse human health or environmental effects.”<sup>25</sup>

### 3.4 OECD SIDS Dossier and SIAR (SIAM 6; June 1997)

MEK has been sponsored through the Screening Information Data Set (SIDS) process, which is essentially equivalent to Tier 1 of the VCCEP Pilot Program. MEK was determined to have “a low order of toxicity” and to be “a low priority for further work.” Copies of the SIDS Dossier and SIAR (Screening Information Assessment Report) are included with this VCCEP submission in Appendix A. The Dossier and SIAR include summaries of all key studies. (Expanded robust summaries of key studies also are included in Appendix B.) The following paragraphs provide an overview of the OECD SIDS assessment process, and summarize key conclusions for MEK.

The SIDS process is part of an international program for collecting and sharing information on certain high production volume chemicals. The SIDS program is sponsored by the Organization for Economic Cooperation and Development (OECD). Once a chemical has been selected for SIDS, a sponsor country collects available data and determines whether or not additional testing is needed to complete the SIDS data set. The SIDS data set includes information on chemical identity, physical characteristics, sources and levels of exposure, environmental fate and pathways, and ecotoxicological and toxicological data. Once a SIDS data set is completed, a SIAR is prepared and discussed at an OECD meeting. The SIAR includes a detailed assessment of all relevant hazard and exposure information, not just the base SIDS data set. Based on the information in the SIAR, OECD makes a determination regarding the need for additional work. EPA represents the United States in the SIDS program.

The United States was the sponsor country for MEK. As part of the OECD SIDS process, the ACC Ketones Panel prepared a SIDS Dossier summarizing the available human health and environmental toxicity data on MEK, as well as information on manufacturing, production and use, exposure, metabolism, and environmental fate and degradation. EPA, as the representative of the sponsoring country, reviewed and commented on this document, which then formed the basis for the MEK SIAR, also prepared by the MEK producers and reviewed and approved by EPA.

The SIAR concluded that MEK should be considered “currently of low priority for further work.”<sup>26</sup>

“The information obtained from this database allows for the characterization of toxicity hazard of MEK for both human/mammalian and environmental effects. Taken together, these considerations support the conclusion that MEK is a low priority for further work.”<sup>27</sup>

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<sup>25</sup> *Id.*

<sup>26</sup> OECD, SIDS Screening Information Assessment Report for Methyl Ethyl Ketone, p. 4 (1997).

<sup>27</sup> *Id.* at 4.

With respect to MEK's toxicity, the SIAR reports that:

- MEK and its metabolic surrogate, 2-butanol, do not appear to present significant risk of adverse reproductive or developmental effects.<sup>28</sup>
- MEK has been shown to be of a low order of toxicity following acute oral, dermal, and inhalation exposure. Contact with the eyes, skin or respiratory tract may produce irritation.<sup>29</sup>
- No significant signs of toxicity were seen following repeated inhalation exposure of rats to MEK at high concentrations.<sup>30</sup>
- MEK has not been shown to have any neurotoxic potential.<sup>31</sup>
- Human volunteers exposed to relatively high levels of MEK did not demonstrate any significant effects, other than minor irritation and sensory effects.<sup>32</sup>
- MEK is not genotoxic and is not likely to be carcinogenic.<sup>33</sup>
- MEK has not been shown to produce skin sensitization.<sup>34</sup>

The SIAR recognizes that MEK is used primarily in commercial and industrial settings, as opposed to consumer products. The SIAR notes that "MEK is widely used as a solvent and as a chemical intermediate. As a solvent, MEK is used in surface coatings, adhesives, inks, traffic marking paint, cleaning fluids, and dewaxing agents."<sup>35</sup> The SIAR concludes that:

- MEK is a high production volume chemical primarily used in commercial and industrial settings.<sup>36</sup>
- Manufacture of MEK takes place in an enclosed process and transport of the material occurs through enclosed systems or bulk carrier. This condition significantly limits exposure during manufacture and handling.<sup>37</sup>
- Fence line concentrations are expected to be negligible.<sup>38</sup>

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<sup>28</sup> *Id.* at 22.

<sup>29</sup> *Id.*

<sup>30</sup> *Id.*

<sup>31</sup> *Id.* at 3.

<sup>32</sup> *Id.*

<sup>33</sup> *Id.*

<sup>34</sup> *Id.* at 22.

<sup>35</sup> *Id.* at 11.

<sup>36</sup> *Id.* at 21.

<sup>37</sup> *Id.*

- Rapid biodegradation in aquatic and terrestrial habitats, and physical degradation in the troposphere occur, indicating that methyl ethyl ketone will not persist in the environment.<sup>39</sup>

The significance of these OECD SIDS activities is two-fold. First, MEK producers have already sponsored MEK on a voluntary basis in an assessment process essentially equal to Tier 1 of the hazard portion of the VCCEP. Second, the OECD SIDS review resulted in a consensus judgment by scientists from the participating countries, based on the hazard assessment, that further testing and evaluation is a low priority. (The OECD assessment does not include extensive assessment of potential children's exposure, on a par with the VCCEP pilot program.)

Secondary-butyl alcohol (sBA or 2-butanol), the direct precursor compound for MEK and a known metabolite of MEK, recently went through the OECD SIDS review process (SIAM 14; March 2002) with its own SIDS Dossier, SIAR, and package of Robust Summaries. The United States was the sponsor country for sBA and, as such, reviewed and commented on all support documentation. Like MEK, the sBA producers sponsored sBA on a voluntary basis, and the review resulted in a consensus judgment by scientists from the participating countries that further testing and evaluation is a low priority because of the low hazard profile of the chemical.

### **3.5 Patty's Toxicology**

The Ketones of Four or Five Carbons Chapter in Patty's Toxicology (Fifth Edition, Volume 6, Morgott, Topping & O'Donoghue, pp. 117-156, 2001) provides extensive discussion of the relevant scientific literature on MEK's potential health effects. The text consists of 39 pages and includes 317 references. Information pertaining to metabolism and toxicokinetics is presented, along with thorough discussions of animal and human data pertaining to the toxicity endpoints of concern to the VCCEP. Some information on environmental concentrations and potential for human exposure also is included. With permission, a copy of the entire Ketones chapter has been included with this submission as Appendix C.

### **3.6 World Health Organization Environmental Health Criteria Document**

The WHO International Programme on Chemical Safety (IPCS) published an Environmental Health Criteria (EHC) document for MEK in 1992. Dr. R. B. Williams of the U.S. EPA Office of Research and Development, who served as one of two co-rapporteurs, prepared the initial draft. The EHC document concludes that "MEK on its own appears a relatively safe organic solvent . . ." (p. 121.)<sup>40</sup> IPCS EHC documents are the product of a rigorous scientific review process (described in the publication). A panel of independent experts reviewed and commented on the draft MEK report, and also attended a multi-day meeting to discuss the draft document.

### **3.7 ATSDR Toxicological Profile**

The Agency for Toxic Substances and Disease Registry (ATSDR) published a toxicological profile of MEK in 1992. Though somewhat dated, the toxicological profile includes information on potential exposures as well as an assessment of hazard data. The document does not

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<sup>38</sup> *Id.*

<sup>39</sup> *Id.* at 3.

<sup>40</sup> The document is available on-line at <http://www.inchem.org>.

include calculation of “minimal risk levels” (MRLs), but does conclude that exposure to MEK “appears relatively innocuous.” (ATSDR, p. 35,1992).

### 3.8 TSCA Testing

The Interagency Testing Committee (ITC) designated MEK for priority consideration for health effects testing under TSCA Section 4(e) in its Fourth Report, published on June 1, 1979.<sup>41</sup> Following publication of the ITC Report, the manufacturers of MEK made additional test data available to EPA, and agreed to conduct a voluntary testing program to fill remaining data needs. On the basis of the Panel’s actions, EPA published a notice on December 29, 1982 in which the Agency announced its preliminary decision not to initiate a rulemaking to require further testing.<sup>42</sup> Specifically, EPA stated that:

“The Agency has concluded that the existing data are sufficient to evaluate some of the effects recommended for testing by the ITC. In other cases, the EPA believes that testing recommended by the ITC is not warranted by the available data. Finally, EPA has tentatively decided to accept the industry proposal in lieu of rulemaking to fill the remaining data gaps of concern to the Agency.”<sup>43</sup>

By that Federal Register notice, EPA removed MEK from the TSCA Section 4(e) priority testing list.<sup>44</sup> In a September 30, 1983 notice in the Federal Register, the Agency affirmed this decision, noting that:

“On the basis of its review and consideration of comments received, the Agency finds no reason to alter its preliminary decision not to propose, at this time, a section 4(a) rule to require health effects testing of . . . MEK.”<sup>45</sup>

Under the voluntary testing agreement to which these notices refer, the Ketones Panel conducted several studies of MEK, including developmental toxicity studies and mutagenicity studies. These studies, in addition to a 90-day inhalation study sponsored by the Chemical Industry Institute of Toxicology, added considerably to the existing body of literature on MEK.

The Agency considered MEK again in 1991 when it issued a proposed test rule under Section 4 of TSCA to require neurotoxicity testing for 10 solvents. In the development of that testing proposal, EPA specifically concluded that further neurotoxicity testing for MEK was not

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<sup>41</sup> See 44 *Fed. Reg.* 31866.

<sup>42</sup> See 47 *Fed. Reg.* 58025 (Methyl Isobutyl Ketone and Methyl Ethyl Ketone; Response to Interagency Testing Committee).

<sup>43</sup> *Id.*

<sup>44</sup> See 56 *Fed. Reg.* 67424, 67428 (December 30, 1991) (noting removals from the TSCA Section 4(e) Priority Testing list).

<sup>45</sup> 48 *Fed. Reg.* 44905 (Methyl Isobutyl Ketone and Methyl Ethyl Ketone Decision to Adopt Negotiated Testing Program).

warranted.<sup>46</sup> In the final rule, EPA reaffirmed its belief that existing neurotoxicity data for MEK were “adequate.”<sup>47</sup>

In an internal Agency memorandum explaining the decision to exclude MEK from the test rule, EPA staff recognized that further neurotoxicity testing of MEK was not scientifically necessary:

“[T]he recommendation to exclude methyl ethyl ketone . . . [and two other compounds] from the initial list of chemicals to be tested is based on the amount of data already available on these compounds. . . . Requiring additional animal studies does not seem necessary. Resources will be better spent on the study of chemicals about which less is known.”<sup>48</sup>

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<sup>46</sup> See 56 *Fed. Reg.* 9105 (March 4, 1991) (Multi-substance Rule for the Testing of Neurotoxicity - Proposed Rule).

<sup>47</sup> 58 *Fed. Reg.* 40262, 40269 (July 27, 1993) (Multi-Substance Rule for the Testing of Neurotoxicity - Final Rule).

<sup>48</sup> See “Selection of Chemicals for Testing Under Neurotoxicity Endpoint Rule,” Memorandum from Suzanne B. McMaster, Toxic Effects Section, Toxic Effects Branch, Health and Environmental Review Division (TS-796) to Gary E. Timm, Chief, Chemical Testing Branch, Existing Chemical Assessment Division (TS-778), U.S. EPA, July 26, 1990.

#### 4. Regulatory Status

MEK must be handled carefully because of its flammability and vapor pressure and the associated dangers of fire or explosion. MEK's status under several environmental, health and safety statutes and regulatory programs is summarized in Table 4.1.

**Table 4.1 MEK Regulatory Status**

Regulation	MEK Status
CERCLA Hazardous Substances	Listed. RQ = 5,000 lbs. (highest category)
RCRA Listed Wastes	Included in DO35 (if the leachate from the TCLP toxicity test contains 200 mg/L or more of MEK). Included in F003 and F005 wastes (spent solvents). Listed as a "U" waste (U159)
EPCRA Extremely Hazardous Substances	Not listed.
EPCRA Toxic Release Inventory	Listed based on status as VOC. <sup>1</sup>
CAA Hazardous Air Pollutants	Removal proposed. <sup>2</sup>
CAA Volatile Organic Compounds	Regulated as a VOC.
CWA Priority Pollutant List	Not listed.
OSHA Z-Tables (Air Contaminants Standard)	Permissible Exposure Limit (PEL) is 200 ppm (590 mg/m <sup>3</sup> ) (8-hour TWA) <sup>3</sup>
ACGIH TLVs (non-regulatory) <sup>4</sup>	Recommended exposure limits are 200 ppm (8-hour TWA) and 300 ppm (885 mg/m <sup>3</sup> ) (15-minute STEL)

<sup>1</sup> See 63 Fed. Reg. 15,195 (Mar. 30, 1998), and discussion in text at Sections 3.2.

<sup>2</sup> See 68 Fed. Reg. 32606 (May 30, 2003).

<sup>3</sup> OSHA revised its PELs for MEK in 1989, as part of a larger air contaminants standard final rule affecting more than 400 substances. The 8-hour TWA was unchanged (200 ppm), but OSHA added a 15-minute STEL of 300 ppm. The 1989 final rule was vacated by the Eleventh Circuit in *AFL-CIO v. OSHA*, 965 F.2d 962 (11<sup>th</sup> Cir. 1992), for reasons unrelated to MEK. The STEL may still apply in states that operate under delegated authority.

<sup>4</sup> The American Conference of Governmental Industrial Hygienists (ACGIH) is not a regulatory body and their limits are "recommended," not required.

MEK has been recognized by the World Health Organization as a food additive/flavoring agent that poses “no safety concern” because it is endogenous in humans as a component of fatty acid and carbohydrate metabolism and because it is “metabolized to or [is an] innocuous [product] *per se*.”<sup>49</sup> MEK also has been approved by the U.S. Food and Drug Administration as a direct food additive for use as a flavoring agent.<sup>50</sup> MEK is also rated as a GRAS (Generally Recognized as Safe) substance (Oser and Ford, 1973).

Under Section 612 of the Clean Air Act, EPA developed a program -- called the Significant New Alternatives Policy (SNAP) program -- to identify acceptable substitutes for chemicals that were being phased out of production because they deplete the stratospheric ozone layer.<sup>51</sup> MEK is listed as an acceptable substitute in a number of applications. In the final SNAP rule, EPA stated that “two of the typical oxygenated hydrocarbons examined in the Agency’s risk screen, methyl ethyl ketone and methyl isobutyl ketone, also have comparatively low toxicity.”<sup>52</sup>

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<sup>49</sup> World Health Organization (1999). *WHO Food Additive Series 42: Safety Evaluation of Certain Food Additives*, pp. 236, 242-243 (1999).

<sup>50</sup> See 21 C.F.R. § 172.515.

<sup>51</sup> 59 Fed. Reg. 13,044 (March 18, 1994).

<sup>52</sup> *Id.* at 13,120.

## 5. Product Overview

This section presents an overview of: (1) production processes; (2) production volume; (3) physical and chemical properties; (4) principal uses; and (5) releases to the environment.

### 5.1 Production Processes

MEK is manufactured in the U.S. in an enclosed, continuous process that converts n-butenes into MEK. In the first section of the process, a mixed butenes stream (30-90+% n-butenes) is contacted with a circulating sulfuric acid-water mixture. Unreacted mixed butenes are sent to the refinery for further processing (if not recycled). Sufficient water is added to the olefin-acid-water mixture to form secondary butyl alcohol (sBA). Some co-products, primarily secondary butyl ether (sBE) and butene dimer (C<sub>8</sub> olefins), also are formed. The sBA and co-products are stripped from the sulfuric acid-water mixture and then separated via distillation. The water is reused in the process or treated in wastewater treatment facilities. The sBA is sold or processed to MEK, the sBE is sold or used in a fuel system and the dimer is sold.

The conversion of sBA to MEK also is accomplished in an enclosed, continuous process. The sBA is heated to reaction temperature in a furnace and passed over a proprietary catalyst where it is dehydrogenated to MEK and hydrogen. Conversions and selectivity to MEK are very high. The MEK is then purified by distillation to remove sBA, water and some heavy ketones. The hydrogen is either sold or used for its co-product value or burned internally at plant facilities. Again, the water is either reused or treated in the wastewater treatment facilities. The heavy ketones are either sold or sent to other units for further processing. The final product (99.5 wt.% MEK) is pumped to tankage and then transported to the customer via tank truck, rail car or marine loading facilities.

### 5.2 Production Volume

The estimated total global capacity in 1999 was approximately 1,065 thousand metric tons; United States production amounted to 260,000 metric tons. Three companies currently produce MEK in the United States: ExxonMobil Chemical Company, Shell Chemical, and Celanese (Chemical Economics Handbook, SRI International, April 2000).

### 5.3 Physical and Chemical Properties

A summary of selected chemical and physical properties of MEK is presented in Table 5.1. Additional information on chemical and physical properties is found in *Patty's Toxicology, Ketones of Four or Five Carbons* Chapter (Table 75.1) (Appendix C), the SIAR (p. 5) (Appendix A), and a product brochure prepared by Celanese (Appendix D).

**Table 5.1 CHEMICAL AND PHYSICAL PROPERTIES OF MEK\***

CHEMICAL NAME:	Methyl Ethyl Ketone
EMPIRICAL FORMULA:	C <sub>4</sub> H <sub>8</sub> O
SYNONYMS:	2-butanone; 2-oxobutane; ethyl methyl ketone; butane-2-one; methyl acetone; and MEK
CAS NUMBER:	78-93-3
APPEARANCE AND ODOR:	Clear, colorless liquid with sharp, sweet odor
MOLECULAR WEIGHT:	72.11
BOILING POINT:	79.6°C
MELTING POINT:	-86.6°C
DENSITY:	0.807 g/mL @ 20°C; 0.799 g/mL @ 25°C***
VAPOR PRESSURE:	77.5 mmHg at 20°C; 91 mmHg @ 25°C****
VAPOR DENSITY:	2.4 (air=1)
FLASH POINT:	-9°C (closed cup); 10°C (open cup)
AUTO IGNITION:	404°C
FLAMMABILITY LIMITS:	1.4 % LL and 11.4 % UL @ 93°C
PARTITION COEFFICIENT:	log K <sub>ow</sub> = 0.29 @ 25°C
(n-Octanol/water)	
CONVERSION FACTORS:	1 ppm = 2.94 mg/m <sup>3</sup> ; 1 mg/L = 340 ppm
SOLUBILITY:	276 g/L at 19.3°C**; 259 g/L @ 25°C***

\* Patty's Toxicology, Fifth Edition, Volume 6, Ketones of Four or Five Carbons, Table 75.1 (Morgott, Topping & O'Donoghue, 2001).

\*\* SIDS Screening Information Assessment Report (1997).

\*\*\* CRC (2000).

\*\*\*\* HSDB (2001).

## 5.4 Uses

MEK is widely used as a solvent and as a chemical intermediate. MEK is used in surface coatings (55%), adhesives (12%), printing inks (4%), chemical intermediates (6%), magnetic tapes (5%) and lube oil dewaxing agents (6%). MEK also is used as an extraction medium for fats, oils, waxes and resins (Chemical Economics Handbook, SRI International, April 2000). These and other uses of MEK are described further in Section 8 (Exposure Assessment), and in a Celanese technical product brochure attached as Appendix D.

## 5.5 Releases to the Environment

EPA's EPCRA Toxics Release Inventory (TRI) database ([www.epa.gov/triexplorer](http://www.epa.gov/triexplorer)) indicates total reported releases of MEK to air, water and land in 2001 were 29,094,942, 47,718; and 124,263 pounds, respectively. Releases of MEK to air, water and land are summarized in the following tables. Table 5.2 indicates the number of facilities that reported air emissions in different reporting ranges. Tables 5.3 and 5.4 summarize releases to water and land, respectively, in 2001.

**TABLE 5.2**

<b>Air Emissions</b>		
<b>No. of Facilities</b>	<b>Reporting Range (lbs/yr)</b>	<b>% Distribution</b>
149	0	8.4
1,047	1 - 10,000	58.9
537	10,001 - 100,000	30.2
43	100,001 - 1,000,000	2.4
2	1,000,001 - 10,000,000	0.1
0	above 10,000,000	0.0
<u>1,778</u>		

Reference: 2001 TRI Data.

**TABLE 5.3**

<b>Releases to Water</b>		
<b>No. of Facilities</b>	<b>Reporting Range (lbs/yr)</b>	<b>% Distribution</b>
1,676	0	94.2
51	1 - 100	2.9
40	101 - 1,000	2.2
11	1,001 - 10,000	0.6
0	above 10,000	0.0
<u>1,778</u>		

Reference: 2001 TRI Data.

**TABLE 5.4**

<b>Releases to Land</b>		
<b>No. of Facilities</b>	<b>Reporting Range (lbs/yr)</b>	<b>% Distribution</b>
1,722	0	96.9
39	1 - 100	2.2
11	101 - 1,000	0.6
3	1,001 - 10,000	0.2
3	above 10,000	0.2
<u>1,778</u>		

**Reference: 2001 TRI Data.**

Because MEK is manufactured in enclosed processes, release to air, land and water from production facilities are low. TRI data for production facilities are summarized in Table 5.5.

**TABLE 5.5**

<b>MEK Releases -- Producers (lbs/yr)</b>			
<b>Facility</b>	<b>Air</b>	<b>Water</b>	<b>Land</b>
Celanese (Pampa, Texas)	70,804	0	0
ExxonMobil Chemical (Baton Rouge, Louisiana)	141,204	761	0
Shell Chemical (Norco, Louisiana)	111,000	0	0

**Reference: 2001 TRI Data.**

As described in Sections 3.3 (Clean Air Act Review) and 8 (Exposure Assessment), EPA evaluated potential exposures from facility releases as part of its review of a petition to remove MEK from the list of hazardous air pollutants (HAPs) maintained under Section 112 of the Clean Air Act. EPA found reasonably anticipated exposures from facility releases to be unlikely to pose any health hazards.

Additional information on sources of MEK in the environment – natural and man-made – and ambient levels detected in various environmental media is presented in Sections 6 and 8.

## 6. Natural Presence in the Environment, Diet and Endogenous Production

MEK is naturally present in the environment through emissions to the atmosphere from such natural sources as European firs, junipers, cedars, cypress trees and ferns (Isidorov *et al.* 1985). It is also naturally present in human blood as a result of endogenous production. MEK is a metabolic byproduct of isoleucine catabolism in humans (WHO 1992; Scriver *et al.* 2001). It is a metabolite of acetoacetyl-CoA and a precursor of propionate. Blood levels of MEK are highly variable as a result of these physiologic mechanisms, and do not appear to reflect environmental exposures (Churchill *et al.* 2001). MEK's volatility makes it difficult to quantify in routine urinalysis, and a quantitative profile of MEK in urine therefore is not available.

In addition, MEK is a natural component of many foods, including apple juice, raw beans, black currants, butte, cabbage, carrots, roasted barley, a variety of cheeses, cream, milk, bread, honey, chicken, tomatoes, potato chips, mushrooms, coffee, eggs, yogurt, roasted nuts, oranges, soy beans, nectarines, smoked fish, black tea, guavas, lingonberries, pears, rum, dried beans, split peas and lentils. (Lande *et al.* 1976; Gordon and Morgan 1979; Lovegren *et al.* 1979; VCF database, 2000; WHO 1992.)

The natural presence of 2-butanol (sBA) in a normal healthy diet also is relevant since MEK is the chief metabolite of 2-butanol. (See Section 7.3 for a discussion on the sBA - MEK metabolism.) 2-Butanol occurs naturally in foods and in beverages as a result of fermentation of carbohydrates, for example in alcoholic beverages (WHO 1987). It has been identified as a volatile component of baked potatoes, Beaufort cheese, roasted filberts, fried bacon, milk, chickpeas, Parma ham, mussels, dry beans, split peas, lentils, barley, Portuguese bagaceiras (grape marcs), and apple and pear juice concentrates (WHO 1992; Urbach 1987; Rembold *et al.* 1989; Hinrichsen and Pedersen 1995; and Lovegren *et al.* 1979). In addition, Shahidi *et al.* (1986) reported the presence of sBA in beef and pork meat.

Additional information on MEK's natural presence in the human diet is presented in Section 8 (Exposure Assessment). It is apparent that children and adults ingest MEK on a regular basis through a normal, healthy diet.

## 7. Hazard Assessment

### 7.1 Introduction

There is an extensive body of literature on the potential health effects from exposure to MEK. The following text summarizes studies deemed most pertinent to the VCCEP Pilot Program.

Most toxicity data listed in Tier 1, Tier 2 and Tier 3 of the Pilot Announcement have been conducted for MEK and/or sec-butanol, or have previously been determined to be scientifically unnecessary. In some cases, multiple studies are available to support an assessment of the toxicity endpoint identified. Conversely, repeated-dose studies provide supporting information for assessments of several toxicity endpoints, including potential reproductive toxicity, neurotoxicity and immunotoxicity.

The specific studies that correspond to each test listed in each tier of the Pilot Announcement are identified in Table 7.1. Individual studies and other relevant data are described further in the following sections of the hazard assessment, organized by VCCEP category. Additional details concerning individual studies are provided in the OECD SIDS Dossier and SIAR (Appendix A) and in expanded robust summaries for selected key studies (Appendix B).

**Table 7.1 Data Requirements for VCCEP Tiers 1-3 and Key Studies Available for MEK**

TIER	TEST	RESULTS <sup>a</sup>
1	Acute Toxicity (Oral)	<p><b><u>Rat</u></b></p> <p>LD<sub>50</sub> Oral Toxicity</p> <p>MEK has a low order of toxicity following single oral exposure.</p> <p><b>LD<sub>50</sub> for MEK is &lt; 1.0 ml/kg (newborns); 3.1 ml/kg (2.5-3.9) 14-day olds; 3.6 ml/kg (2.9-4.4) Young Adults; and, 3.4 ml/kg (2.6-4.4) Older Adults Kimura, et. al. (1971) [Robust Summary (RS) - 1].</b></p> <p><b>LD<sub>50</sub> for MEK is 6.86 ml/kg (5.59 - 8.45). Smyth, et. al. (1962) [RS - 2].</b></p>
1	<b><i>In Vitro</i> Gene Mutation (Bacterial Reverse Mutation Assay)</b>	<p><b><u>In Vitro</u></b></p> <p>Ames Bacterial Mutagenesis Assay</p> <p><b>MEK did not induce reverse gene mutation in bacteria. Zeiger, et. al. (1992) [RS - 3] and Brooks, et. al. (1988) [RS - 4].</b></p> <p>Yeast Mitotic Gene Conversion Assay</p> <p><b>MEK did not induce mitotic gene conversion in yeast. Brooks, et. al. (1988) [RS - 5].</b></p>

TIER	TEST	RESULTS <sup>a</sup>
1	<b>Repeated Dose Toxicity &amp; Reproductive Toxicity (1-Generation)</b>	Superseded by Tier 2 90-Day Subchronic Toxicity and 2-Generation Reproductive Toxicity studies identified below.  <b>Cavender et. al. (1983) [RS - 7] and Cox et. al. (1975) [RS - 8].</b>
1	<b><i>In Vitro</i> Chromosomal Aberrations</b>	<b><i>In Vitro</i></b> Chromosome Aberration Assay  <b>MEK did not induce chromosome damage in RL4 mammalian cells.</b> <b>Brooks et. al. (1988) [RS - 6].</b>
2	<b>90-Day (Subchronic) Toxicity in Rodents</b>	<b><i>Fischer 344 Rats</i></b> 90-Day Toxicity Study  90-day inhalation study at 0, 1250, 2500, or 5000 ppm MEK vapor for 6 hr/day, 5 days/week. No adverse effect on the clinical health or growth of male or female rats except for decrease of mean body weight at 5000 ppm with slight but significant increases in liver weight, liver wt./body wt. ratio, and liver wt./brain wt. ratio. Liver weight changes are considered to be adaptive changes and do not indicate toxic effects. Special neuropathological studies including specimens of the sciatic and tibial nerves and medulla were Epon-embedded and nerves were evaluated by the "teased fiber" method. Histopathological studies including examination of reproductive organs (examined tissues included testes, epididymides, seminal vesicles, vagina, cervix, uterus, oviducts, and ovaries) showed no lesions attributed to MEK exposure. There was no indication that repeated exposure to relatively high levels of MEK had any effect on nerve tissues or reproductive tissues.  <b>No toxic effects were observed at 5000 ppm.</b> <b>Cavender et. al. (1983) [RS - 7].</b>  6-Month Repeated Dose Inhalation Study  Six Males were continuously exposed for 6-months in a Repeated Dose Inhalation Study (22 hr/day to 500 ppm MEK vapor).  <b>Failed to show any significant clinical or histopathological evidence of neurological dysfunction.</b> <b>Egan et. al. (1980) [RS - 19].</b>

TIER	TEST	RESULTS <sup>a</sup>
2	Reproductive and Fertility Toxicity / Effects	<p><b><u>FDRL-Wistar Stock Rats</u></b></p> <p>2-Generation Reproductive Toxicity</p> <p>Combined 2-Generation Reproductive Toxicity and Prenatal Developmental Screen (a developmental screen was performed with the second breeding of the F0 Generation - see below).</p> <p>Dosed daily (ad libitum) for 8 weeks pre-mating and during gestation (females) with sBA (a direct precursor compound to MEK and a known metabolite of MEK - see below).</p> <p>F0 Generation: 0, 0.3, 1.0, or 3.0% solutions (0, 538, 1644, and 5089 mg/kg/day for males and 0, 594, 1771, and 4571 mg/kg/day for females).</p> <p>F1 Generation: 0, 0.3, 1.0, or 2.0% (2.0% calculated to be equivalent to 3384 mg/kg/day for males and 3122 mg/kg/day for females).</p> <p>Maternal NOEL: 1% (~1500 mg/kg/day)  Maternal NOAEL: 1771 mg/kg/day  Pup NOEL: 1% (~1500 mg/kg/day)  Pup NOAEL: 1771 mg/kg/day</p> <p><b>The no-effect level reported by the study researchers was 1.0% (1500 mg/kg/day).</b></p> <p><b>sBA is not a reproductive hazard.</b>  <b>Cox et. al. (1975) [RS - 8].</b></p> <p><b><u>Fischer 344 Rats</u></b></p> <p>Histopathological studies in the 90-Day Subchronic study with MEK included extensive examination of reproductive organs.</p> <p><b>None of the examined tissues (testes, epididymides, seminal vesicles, vagina, cervix, uterus, oviducts, and ovaries) showed lesions attributed to MEK exposure.</b></p> <p><b>Cavender et. al. (1983) [RS - 7].</b></p>

TIER	TEST	RESULTS <sup>a</sup>
2	Prenatal Developmental Toxicity (two species)	<p><b><u>Sprague-Dawley Rats</u></b></p> <p>Exposed to 0, 400, 1000 or 3000 ppm MEK, 7 hr/day, gestation days 6-15.  Maternal NOAEL: 1000 ppm  Maternal LOAEL: 3000 ppm  Pup NOAEL: 1000 ppm  Pup LOAEL: 3000 ppm.</p> <p><b>MEK is not a teratogen.</b>  <b>Deacon et. al. (1981) [RS - 9].</b></p> <p>Exposed to 0, 1000 or 3000 ppm MEK, 7 hr/day, gestation days 6-15.  Maternal NOEL: &gt;3000 ppm  Maternal NOAEL: 3000 ppm  Pup NOAEL: 1000 ppm  Pup LOAEL: 3000 ppm.</p> <p><b>MEK is not a teratogen.</b>  <b>Schwetz et. al. (1974) [RS - 10].</b></p> <p>Exposed to 0, 3500, 5000 or 7000 ppm sBA, 7 hr/day, gestation days 1-20.  Maternal NOEL: &lt; 3500 ppm  Maternal NOAEL: 3500 ppm  Pup NOEL: 3500 ppm  Pup NOAEL: &gt; 7000 ppm.</p> <p><b>sBA is not a teratogen.</b>  <b>Nelson et. al. (1989) [RS - 11].</b></p> <p>FDRL-Wistar Stock Rats (F0 Generation - second breeding):</p> <p>Dosed daily (ad libitum) with sBA at 0, 0.3, 1.0, or 2.0% solutions (0, 538, 1644, and 3384 mg/kg/day for males; 0, 594, 1771, and 3122 mg/kg/day for females) for 8 weeks pre-mating (males and females) and during gestation (females).</p> <p>Maternal NOEL: 1% (1771 mg/kg/day)  Maternal NOAEL : 1% (1771 mg/kg/day)  Pup NOEL: 1% (1771 mg/kg/day)</p> <p><b>sBA is not a teratogen.</b>  <b>Cox et. al. (1975) [RS - 12].</b></p> <p><b><u>Swiss Mice</u></b></p> <p>Exposed to 0, 400, 1000 or 3000 ppm MEK, 7 hr/day, gestation days 6-15.  Maternal NOEL: 1000 ppm  Pup NOEL: 1000 ppm.</p>

TIER	TEST	RESULTS <sup>a</sup>										
		<p><b>MEK is not a teratogen.</b>  <b>Schwetz et. al. (1991) [RS - 13].</b></p>										
2	<p><b><i>In Vivo</i> Mammalian Bone Marrow Erythrocyte Micronucleus Cytogenetic Toxicity</b></p>	<p><b><i>In Vivo</i></b></p> <p>Bone Marrow Erythrocyte Micronucleus Assay</p> <p><b>MEK did not induce increased number of micronucleated polychromatic erythrocytes in CD-1 mice; not mutagenic.</b>  <b>O'Donoghue et. al. (1988) [RS - 15].</b></p>										
2	<p><b>Immunotoxicity</b></p>	<p>White blood cell counts/differentials, gross and histopathological examinations of immune system tissues (lymph nodes and spleen) were performed as part of repeated-dose studies.</p> <p><b>Exposure to MEK vapors at 5000 ppm for 6 hr/day, 5 days/week in a Subchronic Study or a dosage of 1771 mg/kg/day of sBA in a 2-Generation Reproductive Toxicity study showed no indication that immune enhancement or immune suppression takes place. Cavender et. al. (1983) [RS - 7] and Cox et. al. (1975) [RS - 8].</b></p> <p>An immunotoxicity study in CD-1 mice was conducted to evaluate the antibody response to sheep red blood cells (SRBCs) following challenge with acetone (methyl methyl ketone, a structurally similar compound). Time-weighted average dosages (mg/kg/day for 28 days) based on water consumption and actual body weights were:</p> <table border="0" data-bbox="760 1310 1062 1541"> <tr> <td>Vehicle Control</td> <td>0</td> </tr> <tr> <td>Positive Control</td> <td>0</td> </tr> <tr> <td>100 mg/kg/day</td> <td>121</td> </tr> <tr> <td>500 mg/kg/day</td> <td>621</td> </tr> <tr> <td>1000 mg/kg/day</td> <td>1144.</td> </tr> </table> <p>Acetone treatment did not produce any alterations in lymphoid organ weights (spleen or thymus) that were statistically different from controls. No effects were noted for spleen cellularity or Antibody-Plaque Forming Cell (AFC) response following acetone exposures. The AFC responses ranged from 1088 – 1401 AFC/10<sup>6</sup> splenocytes following water or acetone administration, and were not statistically different from control values.</p>	Vehicle Control	0	Positive Control	0	100 mg/kg/day	121	500 mg/kg/day	621	1000 mg/kg/day	1144.
Vehicle Control	0											
Positive Control	0											
100 mg/kg/day	121											
500 mg/kg/day	621											
1000 mg/kg/day	1144.											

TIER	TEST	RESULTS <sup>a</sup>
		<p>Acetone (methyl methyl ketone), a ketone structurally similar to MEK, did not produce immunotoxicity in CD-1 mice. No treatment related effect of acetone on the SRBC antibody response was observed.</p> <p>Woolhiser <i>et. al.</i> (2003) [RS - 14]</p>
2	Metabolism and Pharmacokinetics	<p><b><u>Sprague-Dawley Rats</u></b></p> <p>Metabolism and Pharmacokinetic Study</p> <p>This study supported the estimation by Traiger and Bruckner (1976) that approximately 96% of an administered dose of 2-butanol was oxidized <i>in vivo</i> to MEK. A physiologically based pharmacokinetic model for sBA and its metabolites MEK, 3-hydroxy-2-butanone, and 2,3-butanediol in rats was developed. The model examined the observed blood levels of sBA and the metabolites after oral administration of sBA, and was compared to blood levels of these compounds following oral exposure to MEK. The predicted blood concentrations of sBA and the metabolites were in good agreement with observed data.</p> <p><b>97% of sBA administered orally at 1,776 mg/kg to rats was oxidized via alcohol dehydrogenase to MEK. Equimolar doses of sBA (1,776 mg/kg) produced very similar maximum blood concentrations (C<sub>max</sub>) and areas under the concentration curve (AUC) for both MEK and 2,3-butanediol.</b></p> <p>Dietz <i>et. al.</i> (1981) [RS - 16].</p> <p><b><u>Guinea Pigs</u></b></p> <p>Metabolism and Pharmacokinetic Study</p> <p>2-Butanol, 3-hydroxy-2-butanone, and 2,3-butanediol were identified as metabolites in the serum of guinea pigs injected i.p. with MEK. The initial metabolism of MEK follows both oxidative and reductive pathways to produce 3-hydroxy-2-butanone, 2,3-butanediol and 2-butanol.</p> <p><b>The half-life of MEK in serum was 270 min and the clearance time was 12 hr.</b></p> <p>DiVincenzo <i>et. al.</i> (1976) [RS - 17].</p> <p><b><u>Human</u></b></p> <p>Metabolism and Pharmacokinetic Evaluation</p>

TIER	TEST	RESULTS <sup>a</sup>
		<p>Nine healthy male volunteers were exposed for 4 hr to 200 ppm MEK on 2 separate days at least 1 week apart; one of the exposures constituted sedentary activity and the other encompassed three ergometric exercise periods. Venous blood samples, exhaled air samples, and urine samples were analyzed for MEK and 2,3-butanediol (urine only).</p> <p><b>Two elimination phases were detected for MEK in blood. The T<sub>1/2</sub> for the faster (initial) phase of elimination was 30 min and about 81 min for the slower phase. 2-3% of absorbed dose was eliminated by exhalation. Urinary excretion of unchanged MEK was 0.1% and excretion of the metabolite 2H3B was about 0.1%.</b></p> <p><b>Liira et. al. (1988) [RS - 18].</b></p>
3	<b>Carcinogenicity or Combined Chronic Toxicity / Carcinogenicity.</b>	<p>No specific guideline study. Given lack of genotoxic potential and low order of repeated dose toxicity, MEK is not considered potentially carcinogenic. MEK produced minimal or no systemic effects in laboratory animals following repeated exposures to high doses (5000 ppm, 6 hr/day, 5 days/week for 90 days; 500 ppm MEK vapor for 22 hr/day for up to 6 months).</p> <p><b>MEK has a low order of acute and repeated dose toxicity. The metabolism and pharmacokinetic data for MEK indicates rapid absorption, metabolism and/or excretion as conjugates. Based on the metabolism of sBA and MEK, similar expressions of toxicity, as seen in animals, are expected in humans.</b></p> <p><b>Cavender et. al. (1983); Toxigenics Report (1981) [RS - 7]; Egan et. al. (1980) [RS - 19].</b></p>
3	<b>Neurotoxicity Screening Battery</b>	<p>No specific rodent FOB guideline study. However, MEK was excluded from the TSCA neurotoxicity endpoint test rule based on EPA's conclusion that the neurotoxicity data for MEK were "adequate." Moreover, given the lack of observed clinical neurotoxicity symptoms and lack of neuropathology in rats exposed for 3-6 months, MEK is not considered neurotoxic. Extensive neuropathology was performed on the 90-day and 6-month repeated-dose animals that were also clinically asymptotic.</p> <p><b>Cavender et. al. 1983 [RS - 20], and Egan et. al. 1980) [RS - 19].</b></p> <p>Human behavioral performance tests also showed no</p>

TIER	TEST	RESULTS <sup>a</sup>
		<p>significant neurological effects.</p> <p><b>Dick et. al. 1984, 1988/89, and 1992 [RS – 21, 22 and 23].</b></p> <p><b><u>Fischer 344 Rats</u></b></p> <p>Subset of 5 males and 5 females exposed for 90 days to 0, 1250, 2500, or 5000 ppm MEK vapor for 6 hr/day, 5 days/week, dedicated for special neuropathology in the Repeated Dose 90-day Sub-Chronic Study. Neuropathological studies including specimens of the sciatic and tibial nerves and medulla were Epon-embedded and nerves were evaluated by the “teased fiber” method.</p> <p><b>An extensive neuropathologic investigation did not reveal any lesions that could be attributed to MEK exposure.</b></p> <p><b>Cavender et. al. (1983) [RS - 7].</b></p> <p><b><u>Sprague-Dawley Rats</u></b></p> <p>Males continuously exposed for 6-months in a Repeated Dose Inhalation Study (22 hr/day to 500 ppm MEK vapor). Tissues were sampled from regions of maximum vulnerability determined in previous experimental studies of hydrocarbon neuropathy and included cerebellar vermis, cervicomedullary junction, lumbar cord, dorsal and ventral spinal roots, and spinal ganglia, sciatic notch, and three levels of tibial nerve. The tibial nerves were subjected to the “teased” single fiber technique of evaluation.</p> <p><b>Failed to show any significant clinical or histopathological evidence of neurological dysfunction.</b></p> <p><b>Egan et. al. (1980) [RS - 19].</b></p>
3	<b>Developmental Neurotoxicity</b>	<p>No specific guideline study. MEK was excluded from TSCA neurotoxicity endpoint test rule.</p> <p>Tissue examination of fetuses in multiple guideline-quality developmental toxicity studies showed no indication of a primary effect on the nervous system. Clinical / behavioral observations in long-term (3-6 months) rodent studies and human exposure studies showed no concern for neurotoxicity. Extensive neuropathology was performed on the 90-Day and 6-Month Repeated-dose animals that were also clinically asymptomatic. Human behavioral performance tests also showed no significant neurological effects.</p>

TIER	TEST	RESULTS <sup>a</sup>
		<p><b>Extensive neuropathologic investigation in rodents did not reveal any lesions that could be attributed to MEK exposure and human behavioral performance tests also showed no neurological dysfunction.</b>  <b>Egan <i>et. al.</i> (1980) [RS - 19]; Cavender <i>et. al.</i> (1983) [RS - 20]; Dick <i>et. al.</i> (1984, 1988/89, and 1992) [RS - 21, 22 and 23].</b></p> <p><b>Three developmental toxicity studies with MEK in 2 species showed no evidence of neurological malformation.</b></p> <p><b>Schwetz <i>et. al.</i> (1991) [RS - 13], Deacon <i>et. al.</i> (1981) [RS - 9], and Schwetz <i>et. al.</i> (1974) [RS - 10].</b></p> <p><b>Two developmental toxicity studies with sBA in rats showed no evidence of neurological malformation.</b>  <b>Nelson <i>et. al.</i> (1989) [RS - 11] and Cox <i>et. al.</i> (1975) [RS - 12].</b></p>
Human Experience	Human Behavioral Performance Tests	<p><b><u>Humans</u></b></p> <p>4-Hr exposures to MEK (200 ppm) were conducted to assess the sensitivity of the neurobehavioral tests in 97 males and 44 females. Participants were tested repeatedly for alertness during the approximately 8 hours of testing. Three different behavioral tasks with 28 measurements per individual were evaluated. To determine body burden of MEK, four alveolar breath samples were collected: pre-exposure; during exposure; at the end of exposure; and, 90-min post exposure. Venous blood was drawn 2 hr after exposure began and immediately at the end of the 4-hr exposure.</p> <p><b>MEK at 200 ppm produced no significant effects in any of the behavioral performance tests used in this study.</b>  <b>Dick <i>et. al.</i> (1984) [RS - 21].</b></p> <p>4-hr. exposures to MEK (200 ppm) were conducted to assess biochemical and behavioral performance changes in 12 males and 13 females. Subjects were tested through 10 hr. with the following neurobehavioral tests: 4 psychomotor (Visual-Vigilance, Dual Task, Choice Reaction Time, and</p>

TIER	TEST	RESULTS <sup>a</sup>
		<p>Sternberg Short-Term Memory Scanning); 1 sensorimotor (Postural Sway); and 1 psychological test (Profile Of Mood States - POMS).</p> <p><b>Exposures to 200 ppm MEK showed no statistically significant results in neurobehavioral tests.</b></p> <p><b>Dick et. al. (1988/89) [RS - 22].</b></p> <p>4-hr. exposures to MEK (200 ppm) were conducted to assess biochemical and behavioral performance changes in 13 males and 10 females. Subjects were tested with the following neurobehavioral tests: 5 psychomotor (Choice Reaction Time [CRT], Simple Reaction Time [SRT], Visual-Vigilance, Dual Task [auditory tone discrimination and tracking], and Sternberg Short-Term Memory Scanning); 1 neurophysiological test (Eye Blink Reflex); 1 sensorimotor (Postural Sway); and 1 psychological test (Profile Of Mood States - POMS).</p> <p><b>Behavioral performance tests showed no significant neurological effects.</b></p> <p><b>Dick et. al. (1992) [RS - 23].</b></p>

<sup>a</sup> Robust Summaries (RS - 1 through 23) for these key studies are provided in Appendix B .

## 7.2 Acute Toxicity (Tier 1)

The potential acute toxicity of MEK has been extensively studied. Animal studies have focused primarily on lethality, narcosis and sensory irritation, and have been conducted in multiple species (rats, mice, rabbits) and by multiple routes of administration (oral, inhalation, dermal, parental exposure). The available data demonstrates MEK has low acute toxicity. No further evaluation of potential acute oral or inhalation toxicity of MEK in animals is warranted at this time.

MEK was ranked as “slightly toxic” based upon a summary of acute lethality studies conducted by the oral and pulmonary routes (Kennedy and Graepel, 1991). MEK has excellent warning properties with an odor threshold of about 5 ppm (Amoore and Hautala, 1983).

Estimates of the acute oral LD<sub>50</sub> in rats range from approximately 2.5 to 5.6 g/kg (Kimura *et al.* 1971; Smyth *et al.* 1962). Topping *et al.* (1994) identified oral LD<sub>50</sub>s in rats of between 3 and 7 mL/kg. An oral LD<sub>50</sub> in mice of 4.05 g/kg was reported by Tanni *et al.* (1986), which is comparable to the 3.14 g/kg 24-hour oral LD<sub>50</sub> in mice reported by Zakhari and Snyder (1977). Estimates of the acute dermal LD<sub>50</sub> for rabbits range from greater than 5.0 g/kg (Opdyke 1977) to 13 g/kg (Panson and Winek 1962), with Smyth *et al.* (1962) reporting an intermediate value of 8.0 to >10.0 g/kg.

There have been several attempts to estimate the acute inhalation LC<sub>50</sub> in guinea pigs. In the first of these studies (Patty *et al.* 1935), guinea pigs tolerated 10,000 ppm for up to 13 hours, and no effects were seen at 3,300 ppm. In a second guinea pig study, the 4-hour inhalation LC<sub>50</sub> was found to be between 10,000 and 33,000 ppm (Specht 1940).

Two inhalation studies in rats indicate 8-hour LC<sub>50</sub> values of approximately 8,000 ppm (Pozzani *et al.* 1959; Smyth *et al.* 1962). A 4-hour, 14-day LC<sub>50</sub> of 11,700 ppm was reported in mice by LaBelle and Brieger (1955), while Zakhari *et al.* (1977) reported a 45-minute LC<sub>50</sub> in mice at 69,400 ppm. In an earlier study (Carpenter *et al.* 1949), the two-hour LC<sub>50</sub> in Sherman rats was estimated to be between 2,000 and 4,000 ppm. It is likely, however, that the lower value reported in the Carpenter study was an error, since a more recent study demonstrated exposure of rats to MEK at 1250, 2500 or 5000 ppm for 6 hours/day, 5 days/week for 90 days was minimally toxic (Cavender *et al.* 1983). In a second study, exposure to 10,000 ppm was not lethal over a period of “a few” (actual number unspecified) days (Altenkirch *et al.* 1978). Similarly, Smyth *et al.* (1962) reported that rats exposed to 2000 ppm for 2 hours showed no apparent signs of toxicity. Thus, the best estimate is that the 4-hour inhalation LC<sub>50</sub> in rats exceeds 5,000 ppm and may exceed 10,000 ppm.

The dermal toxicity of MEK also has been evaluated. The rabbit dermal LD<sub>50</sub> has been reported at greater than 5 g/kg (Opdyke 1977), greater than 10 g/kg (Smyth *et al.* 1962), and 13 g/kg (Panson and Winek 1980). MEK has relatively low dermal irritancy potential. Smyth *et al.* (1962) rated MEK as a 2 out of a possible 10 for dermal irritancy to albino rabbits. Weil and Scala conducted an interlaboratory comparison of the skin irritancy of solvents to albino rats. Twelve of the 22 laboratories rated MEK as a skin irritant, with irritancy values ranging from 0 to 3.2 out of a possible 30.

MEK was not a contact allergen in the mouse ear-swelling test (Descotes 1988). There was no evidence of MEK-induced skin sensitization of Hartley albino guinea pigs in a study where MEK was used as the vehicle control/solvent (Cannelongo *et al.* 1978).

No sensitization reactions were seen in human volunteers exposed to a 20% MEK in petrolatum mixture (Epstein 1975). No irritation was seen following a 48-hour closed-patch test in humans.

In sum, MEK's acute toxicity has been well tested in multiple species and by multiple routes of exposure. EPA has concluded, “[a]vailable data indicate that MEK has low acute toxicity.”<sup>53</sup> Accordingly, no further evaluation is warranted at this time.

### **7.3 Metabolism and Pharmacokinetics (Tier 2)**

Absorption of MEK is rapid via dermal contact, inhalation, ingestion and intraperitoneal injection. It is rapidly transferred into the blood and hence to other tissues. The solubility of MEK appears similar for all tissues. The clearance of MEK and its metabolites in mammals is essentially complete in 24 hours. MEK is metabolized in the liver, where it is primarily oxidized to 3-hydroxy-2-butanone and subsequently reduced to 2,3-butanediol. A small portion may be reduced to 2-butanol, but 2-butanol is rapidly oxidized back to MEK. The bulk of MEK taken into the mammalian body enters the general metabolism and/or is eliminated as simple compounds such as carbon dioxide and water. Excretion of MEK and its recognizable metabolites is mainly through the lungs, although small amounts are excreted via the kidneys. The pharmacokinetics and metabolism of methyl ethyl ketone (MEK) and secondary butyl alcohol (sBA or 2-butanol;

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<sup>53</sup> 63 Fed. Reg. 15195, 15197 (March 20, 1998) (see Section 3.2).

metabolic precursor of MEK) are interrelated and toxicology data sets indicate that each is a good surrogate for the other. A complete data set is available for sec-Butanol (sBA) on the following endpoints: acute toxicity (oral, inhalation, dermal), irritation studies (skin, eye and respiratory tract), reproductive toxicity, developmental toxicity and genotoxicity assays (OECD 2002).

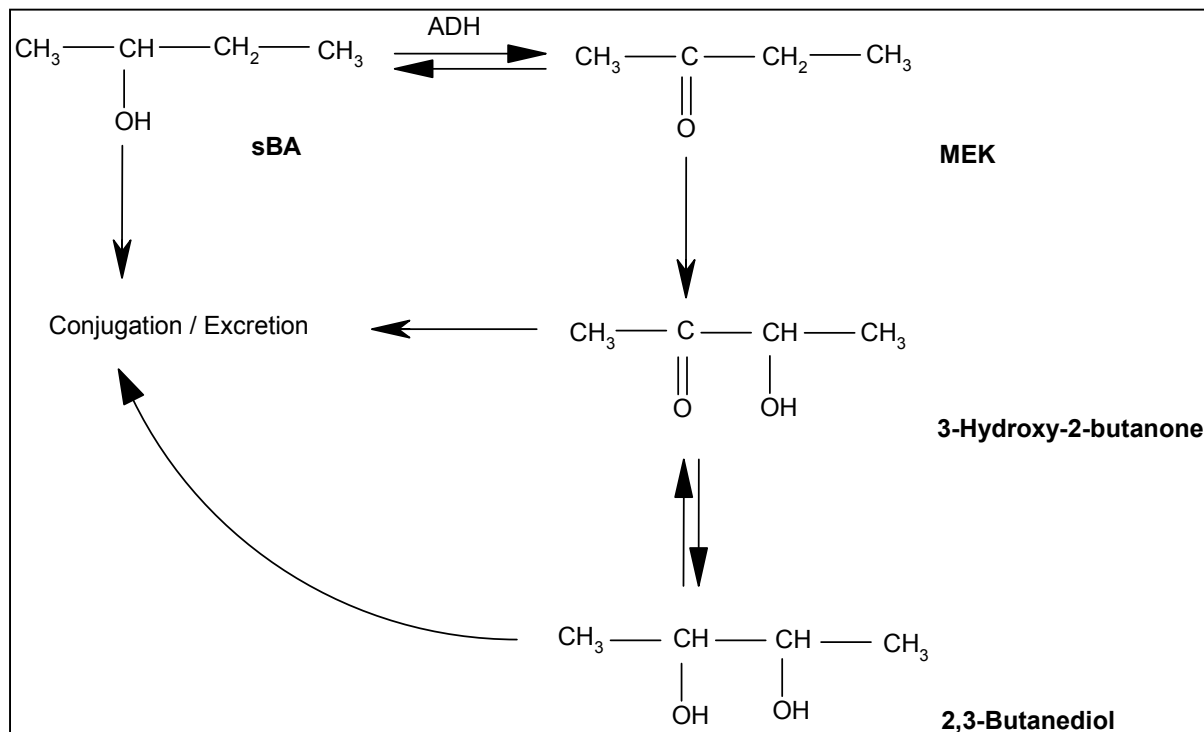
The metabolic relationship between sBA and MEK, established in pharmacokinetic studies, indicates that sBA is rapidly absorbed, partly excreted as conjugates, but mostly metabolized to MEK. The MEK is subsequently converted to metabolites that are exhaled, excreted in the urine, or incorporated into endogenous metabolism. Based on this metabolic relationship, the toxicities of sBA and MEK in animals are considered to be very similar. It is assumed that the metabolic relationship between sBA and MEK in humans will be similar to that in rats.

MEK and sBA have similar pathways of metabolism. In experimental animals, sBA is rapidly metabolized to MEK as shown by blood levels of MEK following oral exposure. Both, MEK and sBA, further generate similar levels of the metabolites 3-hydroxy-2-butanone (3H - 2B) and 2,3-butanediol (2,3 - BD).

The major metabolic change that ketones (*i.e.*, MEK) undergo is reduction to the corresponding secondary alcohol (e.g., sBA) that is usually eliminated combined with glucuronic acid. Oxidation of MEK appears to proceed by hydroxylation forming 3-hydroxy-2-butanone and by reduction at the carbonyl group forming the secondary alcohol, 2-butanol. The 3-hydroxy-2-butanone is further reduced to a diol and is not appreciably oxidized to a dione. The hydroxylation products are eliminated in urine as o-sulfates or o-glucuronides or may enter the intermediary metabolism to be eliminated as CO<sub>2</sub> or incorporated into tissues (DiVincenzo et al. 1976).

The following metabolic scheme is proposed (Figure 7.3.1):

**Figure 7.3.1 Metabolic Pathways of MEK**



Source: ECETOC sec-Butanol Task Force Joint Assessment of Commodity Chemicals; used in sec-butanol OECD SIDS SIAR (as described by DiVincenzo *et al.*, 1976).

Dietz and co-workers (1981) found that 97% of 2-butanol (sBA) administered orally to rats was converted to MEK. MEK subsequently was metabolized to sBA, 3-hydroxy-2-butanone (3H-2B), and 2,3-butanediol (2,3-BD) in both rats and guinea pigs (DiVincenzo *et al.* 1976; Dietz *et al.* 1981). Serum metabolites in humans have not been identified; however, after exposure to MEK by inhalation, 3% of the administered MEK dose was excreted unchanged in the expired air and 2% was excreted in the urine as 2,3-butanediol (Liira *et al.* 1988). Since a relatively small amount of the MEK parent compound or known metabolites were recovered, it was assumed that the majority of the MEK was metabolized to low molecular weight compounds and re-incorporated into other molecules during biosynthetic processes.

In a study by DiVincenzo *et al.* (1976) male guinea pigs were given a single i.p. dose of 450 mg/kg MEK dissolved in corn oil (25% solution). Blood samples were collected over 16 hours and analyzed for concentrations of MEK and its metabolites. Since MEK is water-soluble, it is likely to be well absorbed and distributed throughout the body water compartment. Over 90% of the aliphatic ketone was distributed in the plasma fraction and half-lives in serum were estimated by extrapolating the linear portion of the decay curve to zero time. The half-life of MEK in serum was 270 minutes. The clearance time of MEK was 12 hours and the clearance time of the three metabolites, sBA, 3H-2B, and 2,3-BD was 16 hours.

As noted above, sBA is metabolized to MEK, and MEK is metabolized to 3H-2B, 2,3-BD or back to sBA. In order to gain insight into the time course interrelationships of sBA and its metabolites

and to accurately define the role of the metabolites in CCl<sub>4</sub> -induced hepatotoxicity (Dietz and Traiger 1979; Traiger and Bruckner 1976), a study was conducted to determine the degree of biotransformation for sBA or MEK.

Dietz *et al.* (1981) selected doses for MEK and sBA based on the earlier pharmacokinetic analysis that established approximately 97% of an administered dose of sBA was oxidized *in vivo* to MEK. Male rats were given equimolar oral doses of sBA (2.2 ml/kg; 1776 mg/kg as a 22% aqueous solution) or MEK (2.1 ml/kg; 1690 mg/kg as a 21% aqueous solution), and serial blood samples were collected over time. Equimolar doses (1,776 mg/kg/bw) of sBA and MEK produced very similar maximum blood concentrations ( $C_{max}$ ) and areas under the concentration curve (AUC) for both MEK and 2,3-butanediol as shown below.

**Table 7.2**

<b>Peak Blood Concentrations of sBA, MEK and Metabolites in Rats</b>				
<b>Following oral sBA dose<sup>a</sup></b>				
	sBA	MEK	3-hydroxy-2-butanone	2,3-butanediol
PEAK (mg/ml)	0.59 (2 h)	0.78 (8 h)	0.04 (12 h)	0.21 (18 h)
AUC (mg hr/L)	3254	9868	443	3167
<b>Following oral MEK dose<sup>b</sup></b>				
	MEK	sBA	3-hydroxy-2-butanone	2,3-butanediol
PEAK (mg/ml)	0.95 (4 h)	0.033 (6 h)	0.027 (8 h)	0.26 (18 h)
AUC (mg hr/L)	10, 899	414	382	3863

<sup>a</sup> 1,776 mg sBA/kg, or 2.2 ml/kg of a 22% aqueous solution

<sup>b</sup> 1,690 mg MEK/kg, or 2.1 ml/kg of a 21% aqueous solution

In the sBA-treatment phase of the study, blood concentrations of sBA and its metabolites MEK, 3H-2B, and 2,3-BD were measured. Blood sBA concentrations of 0.59 mg/ml peaked at 2 hours and declined to less than 0.05 mg/ml at 16 hours. The MEK concentration of 0.78 mg/ml peaked at 8 hours. As the sBA concentration fell, the end metabolite, 2,3-BD, concentration rose to a maximum of 0.21 mg/ml at 18 hours.

Following an oral dose of MEK, blood concentrations of MEK and its metabolites sBA, 3H-2B, and 2,3-BD were measured. Blood MEK concentrations of 0.95 mg/ml peaked at 4 hours and declined to less than 0.077 mg/ml at 18 hours. As the MEK concentration fell, the end metabolite 2,3-BD rose to a maximum concentration of 0.26 mg/ml at 18 hours.

The Dietz study supported the hypothesis that no significant difference in the AUC for MEK occurs after dosing with either 1776 mg/kg sBA or 1690 mg/kg of MEK (9868 mg hr/L vs. 10, 899 mg hr/L). Also, the 2,3-BD end metabolite concentrations peaked after 18 hours at similar levels (0.21 mg/ml from sBA and 0.26 mg/ml from MEK). In summary:

- Approximately ninety-seven percent of the sBA administered orally to rats was converted to MEK.
- MEK, like sBA, was metabolized to an intermediate metabolite, 3H-2B, and subsequently to an end metabolite, 2,3-BD.
- Male rats dosed with sBA (105 % of an MEK dose; volume/body weight) showed an AUC for MEK in blood that was comparable to rats dosed with MEK.

- The peak concentrations and total amount (AUC) of the metabolites 3H-2B and 2,3-BD were similar following sBA or MEK exposure.

If toxicity or biologic effect is dependent on total MEK availability (AUC), then whether one doses with sBA or MEK makes little difference. The quantity of MEK derived from sBA-dosing is very similar to that derived from MEK-dosing. However, when dosed directly, MEK is available at an earlier time than when dosing with sBA.

In a study with human volunteers (Liira *et al.* 1988), relative pulmonary uptake of MEK was about 53% throughout a 4-hour inhalation exposure period at 200 ppm. Blood concentrations of MEK rose steadily throughout the exposure period. Only 3% of the absorbed dose was excreted unchanged by exhalation. The high blood and tissue solubility of MEK may account for the high and constant retention of MEK in the lungs. The input of MEK to the tissues showed a continuously increasing blood MEK concentration indicating no steady state was reached.

The end metabolite 2,3-BD, as seen in the animal studies, was detected in the urine with maximum rates of excretion at about 6-12 hours from the beginning of exposure. About 2% of the MEK dose taken up by the lungs was excreted as 2,3-BD. The main portion of the inhaled MEK was thought to metabolize via uncharacterized metabolic pathways. It was speculated that the greater part of the absorbed MEK was probably converted to acetate or acetoacetate via the 3H-2B intermediate metabolite.

Saito (1975) administered 2 ml/kg sBA (approximately 1.6 g/kg) orally to rabbits and blood samples were collected and analyzed by gas chromatography. Approximately 1 mg/ml sBA was found in blood after 1 hour, with 0.7 mg/ml present after 7 hours, and only trace amounts after 10 hours. sBA was metabolized via alcohol dehydrogenase to MEK, which was detected in the blood, reaching its maximum level in the blood after 6 hours. sBA was excreted via exhalation (3.3% of the original dose) and urine (2.6%), but more of the original sBA was excreted as its metabolite MEK.

MEK excretion via exhalation and urine were 22.3% and 4.1% of the original dose, respectively. In another study, 14% of an 8 mmol/kg [approximately 600 mg/kg] oral dose of sBA in rabbits was excreted in the urine as a glucuronic acid conjugate (Kamil, 1952 as cited by Williams, 1959). The majority of the remaining dose was metabolized to MEK.

The metabolic relationship of MEK and sBA, shown above, indicates the MEK and sBA toxicology data sets are good surrogate profiles for each other.

#### **7.4 Gene Mutation and Cytogenetics (Tiers 1 and 2)**

MEK has been shown to be without genotoxic activity in a variety of short-term tests. MEK and the metabolically related 2-butanol were not mutagenic to the bacteria, *Salmonella typhimurium* and *Escherichia coli*, with and without metabolic activation; did not induce mitotic gene conversion in the yeast, *Saccharomyces cerevisiae*; or cause chromosome damage in mammalian cells (cultured rat liver cells) (Brooks *et al.* 1988). MEK had no effect in the Salmonella/microsome assay, mouse lymphoma assay, BALB/3T3 mouse embryo cell transformation assay, unscheduled DNA synthesis in rat primary hepatocytes, and in the *in vivo* mouse micronucleus assay (O'Donoghue *et al.* 1988). MEK also did not produce chromosomal aberration in rat liver cells (*in vitro*) or mouse bone marrow (*in vivo*) or DNA damage

(unscheduled DNA synthesis in rat hepatocytes) (NTP Fiscal Year 1987 Annual Plan; Florin *et al.* 1980; Marnett *et al.* 1985; Nestmann *et al.* 1980; Perocco *et al.* 1983; Shirasu 1976).

MEK, at a concentration of 3.54%, induced chromosomal malsegregation, characterized as aneuploidy, in *Saccharomyces cerevisiae* but did not induce mitotic recombinations or point mutations (Zimmermann *et al.* 1985). However, the protocol involved cold storage on ice for periods up to 17 hours after treatment for 4 hours, and aneuploidy was only observed after incubation on ice. This storage at ice-cold temperature may have been involved in the response. A number of chemicals have been shown to induce aneuploidy, many of which do not induce other detectable genetic effects (e.g., mutation or recombination). Thus, chemically induced chromosomal malsegregation might be the result of damage or alteration to different targets from those leading to mutation (*i.e.*, the primary targets were not DNA or the DNA-metabolizing systems). Microtubules are candidate targets for aneuploidy induction. Other investigators have reported negative genotoxicity studies of MEK in bacteria (Shimizu *et al.* 1985; Zeiger *et al.* 1992). The clastogenicity of MEK was investigated in the *in vivo* micronucleus assay by administering 10 mL/kg of MEK to male and female Chinese hamsters (i.p.) and failed to show any mutagenic effect (Basler, 1986).

In sum, MEK has been tested in a wide battery of mutagenicity assays and the weight-of-the-evidence is that MEK is not mutagenic. See, e.g., EPA, *Toxicological Review of Methyl Ethyl Ketone*, p. 47 (September 2003) (“MEK is not mutagenic as indicated by a number of conventional short-term assays for genotoxic potential.”); EPA, CAA Proposed Rule, 68 Fed. Reg. 32606, 32613 (May 30, 2003) (“Methyl ethyl ketone has been tested for activity in an extensive spectrum of *in vitro* and *in vivo* genotoxicity assays and has shown no evidence of genotoxicity in most conventional assays . . . Overall, studies of MEK yield little or no evidence of genotoxicity.”); ATSDR, *Toxicological Profile for 2-Butanone*, p. 36 (1991) “It appears, therefore, that 2-butanone alone is not genotoxic to humans.”; OECD, *SIDS Screening Information Assessment Report for Methyl Ethyl Ketone*, p. 3 (1997) (“MEK is not genotoxic and is not likely to be carcinogenic”). No further evaluation of MEK’s genotoxic potential is warranted at this time.

## 7.5 Subchronic Studies (Tier 2)

Cavender *et al.* (1983) report the results of a 90-day inhalation study in rats at 0, 1250, 2500, or 5000 ppm MEK vapor for 6 hr/day, 5 days/week. Rats were observed daily for clinical signs and mortality, weekly for food consumptions and body weight, and at the end of the exposure period for neurological function and ophthalmologic effects. Clinical pathological evaluations (urinalysis, hematology and serum chemistry) were conducted on 10 animals per sex and exposure group, as was gross pathology and histopathology at study termination.

There were no signs of nasal irritation during the study and ophthalmologic examinations were negatives at all exposure concentrations. The study found a slight (not exceeding 8% as compared to the control group) and transient depression in body weight gain in the high dose group. In addition, the 5000 ppm (high dose) female exposure group experienced slight but significant increases in liver weight, liver weight to body weight ratio, and liver weight to brain weight ratio at necropsy, while high dose male rats experienced increased absolute and relative liver weights only. No accompanying histopathological lesions were observed; as a result, the authors concluded that the organ weight changes were the result of physiological adaptation mechanisms, rather than an indication of toxic effects.

Special neuropathological and routine pathological studies, including examination of reproductive organs, did not reveal any lesions that could be attributed to MEK exposure. No effects were seen in serum chemistry, urine chemistry or blood hematology except for females in the high dose group, which experienced increases in serum potassium, glucose and alkaline phosphatase activity, and decreased alanine aminotransferase activity.

The study researchers identify 5000 ppm as the NOAEL in this study. The MEK SIAR similarly concludes that 5000 ppm is the study NOAEL. The final IRIS Toxicological Review of MEK does not formally specify a LOAEL/NOAEL, but acknowledges the absence of any clearly adverse effects at the top dose of 5000 ppm, stating (p. 54):

A subchronic inhalation study of MEK found no persistent body weight changes, gross behavioral changes, or histological changes in major tissues and organs in rats exposed 6 hours/day, 5 days/week for 90 days to concentrations as high as 5,000 ppm (14,750 mg/m<sup>3</sup>) (Cavender *et al.* 1983). Some changes in organ weight (including increased liver weight and decreased brain weight) and clinical pathology parameters were observed; however, these were not supported by histological changes.<sup>54</sup>

LaBelle and Brieger (1955) evaluated the effects on rats and guinea pigs exposed to 235 ppm MEK 7 hours/day, 5 days/week for 12 weeks. The study included histopathological examinations and evaluation of growth. The researchers report a decrease in body weight gain in the MEK-exposed rats, but do not provide statistics or standard deviation. No adverse effects were reported in guinea pigs.

There are numerous other subchronic inhalation studies on MEK, but these studies have focused primarily on neurotoxicity as an endpoint and thus are discussed in Section 7.10.

EPA has concluded that MEK has low systemic toxicity, stating “Available data indicate that MEK has low chronic toxicity. . . . [S]everal well-designed repeated dose oral and inhalation studies in laboratory animals demonstrate low systemic toxicity with MEK.”<sup>55</sup> Similarly, the SIAR for MEK concludes that “[n]o significant signs of toxicity were seen following repeated inhalation exposure of rats to MEK at high concentrations.” (OECD 1997, p. 22). There does not appear to be any need for further subchronic testing of MEK at this time.

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<sup>54</sup> In its draft *Toxicological Review of Methyl Ethyl Ketone* (March 2003), EPA concluded that 5000 ppm was a LOAEL and 2500 ppm was the NOAEL in this study. The American Chemistry Council Ketones Panel explained in its comments on the draft IRIS review that the Agency’s tentative interpretation was not scientifically appropriate; a change in liver weight, for example, unaccompanied by any evidence of pathology, should not be considered an adverse effect. A copy of the Panel’s comments on the IRIS update is provided at Appendix F. In the final Toxicological Review, NCEA dropped its characterization of 5000 ppm as a LOAEL. See main text at pp. 28-30 and p. 54, and Appendix A at p. A-18: “The text was revised to further emphasize the difficulty in interpreting the significance of these findings. In light of these uncertainties, characterization of the 5,000 ppm exposure level as a LOAEL and the mid-dose group (2,518 ppm) as a NOAEL were dropped.”

<sup>55</sup> 63 Fed. Reg. 15195, 15197 (March 30, 1998) (MEK EPCRA decision).

## 7.6 Reproductive Toxicity (Tiers 1 and 2)

Classic reproductive effect studies have not been conducted with MEK. Results of subchronic inhalation studies do not indicate that the reproductive organs of either sex are likely target organs for MEK. In the study by Cavender *et al.* (1983), histological examination of the testes, epididymides, seminal vesicles, vagina, cervix, uterus, oviducts, ovaries, and mammary glands of rats exposed to MEK at concentrations up to 5,000 ppm for 90 days revealed no exposure-related lesions. In addition, the reproductive effects of 2-butanol have been evaluated in a two-generation reproductive study. As described in Section 7.3, 2-butanol is rapidly converted to MEK, such that 2-butanol toxicity studies are useful for evaluating the potential toxicity of MEK.

In the two generation reproduction study, male and female Wistar rats were exposed to sec-butanol (sBA) at 0, 0.3, 1.0 or 3.0% in drinking water (Cox *et al.* 1975). After 9 weeks of exposure, the parental animals were mated. Significant effects were noted in the F<sub>1A</sub> litters from the 3% group, including reduced number of live pups, pup viability, and mean body weights at 4 and 21 days. Based on these effects, the 3% sBA dose was decreased to 2%. Following a 2 week adaptation period, the P generation subsequently was remated to produce a second litter (F<sub>1B</sub>) and the F<sub>1A</sub> animals were selected for an F<sub>2</sub> mating. Similar effects were seen in the F<sub>1B</sub> pups as in the F<sub>1A</sub> pups, though the severity was reduced.

At both the 0.3% and 1.0% level, sBA was not toxic in terms of growth and reproduction efficiency; however, at 2.0%, sBA caused a significant depression in growth of weanling rats. Gross and microscopic pathologic findings were negative for the two lower dose levels, being limited to those frequently seen in untreated rat colonies. The 2.0% level resulted in a series of mild changes in the rat kidney, which, while not suggestive of overt toxicity, appeared to represent responses to stress. No other findings of note were seen. sBA produced no effects when administered to rats in the drinking water up to the level of 1% (equivalent to 1771 mg/kg/day). The 2% dose level caused effects suggesting mild toxicity and/or stress reactions. There was no observed reproductive toxicity in parental animals. The 2.0% group offspring had a significant depression in growth of weaning rats. sBA was somewhat fetotoxic at the 2.0% dose level, as shown by decreased mean pup weights. This was a minimal response as shown by the fact that none of the other parameters (nidation, early or late fetal deaths) were detectably affected. Skeletal abnormalities seen in the sBA groups were consistent in type and frequency with the spontaneous incidence observed in this rat colony. There were no significant soft tissue findings in the 2% treated group (FDRL, 1975, unpublished report). The LOAEL in this study was 3,122 mg/kg/day (2% solution), and the NOAEL was 1,771 mg/kg/day (1% solution). (See IRIS Toxicological Review of Methyl Ethyl Ketone, p.39, p. 62 (Table 5).<sup>56</sup>

As already described, the oral RfD in the IRIS update for MEK is based on the Cox study. EPA calculated several benchmark dose levels associated with decreased fetal body weight and identified the lowest (657 mg/kg/day) as its point of departure. NCEA made a molar adjustment to account for the difference in molecular weights between MEK and sBA, yielding a point of departure of 639 mg/m<sup>3</sup>, and then applied total uncertainty factors of 1000 to derive an RfD of 0.6 mg/kg/day. For reasons explained in Section 7.13, this should be considered a conservative value.

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<sup>56</sup> The draft Toxicological Review identified 1771 mg/kg/day as a LOAEL, based on fetal body weight reductions seen in F<sub>1A</sub> pups that were not statistically significant and also not seen in F<sub>2</sub> pups. This interpretation represented a departure from previous EPA assessments of the study. As noted in the text, the final Toxicological Review corrected this interpretation and identified 1771 mg/kg/day as a NOAEL. See Toxicological Review Appendix A, pp. A-13 and A-15.

EPA has concluded that “the available data indicate that MEK is not likely to be a reproductive toxicant,”<sup>57</sup> and that “the concern for reproductive toxicity appears to be low.”<sup>58</sup> Similarly, the MEK SIAR reports that MEK does “not appear to present significant risk of adverse reproductive . . . effects.” (OECD 1997, p.3). No further reproduction studies of MEK appear to be warranted at this time.

## 7.7 Developmental Toxicity and Teratogenicity (Tier 2)

Three studies were conducted in laboratory animals to investigate the developmental effects of MEK (Schwetz *et al.* 1974; Deacon *et al.* 1981; Schwetz *et al.* 1991). The studies exposed rats or mice to MEK (400-3000 ppm range) for 7 hours/day on days 6-15 of gestation. It is well known, via metabolism studies, that 96% of sBA administered orally to rats is rapidly converted to MEK (Dietz *et al.* 1981 and DiVincenzo *et al.* 1976). Therefore, two sBA developmental studies should also be considered as pertinent when assessing the teratogenicity / fetal toxicity of MEK (Gallo *et al.* 1977; Nelson *et al.* 1989).

The earliest study (Schwetz *et al.* 1974), conducted in Sprague-Dawley rats exposed by inhalation to 1000 or 3000 ppm MEK, found no statistically significant effects on the number of implantations or fetal resorptions, the average litter size, or the conception rate. The reported effects included significantly reduced fetal body weight and fetal crown-rump length at 1000 ppm. The total number of litters with fetuses showing skeletal anomalies was significantly increased following exposure to 1000 ppm but not at the 3000 ppm exposure level. At 3000 ppm, there was a statistically significant increase in the total number of gross and soft tissue abnormalities and an increase in the number of fetuses with delayed ossification. The authors concluded that MEK was embryotoxic / fetotoxic, and potentially teratogenic to rats. However, the incidence of major malformations was low enough to regard the teratogenic effects as questionable. No signs of maternal toxicity were reported and the fetal results observed were not confirmed in subsequent studies.

A follow-up study, to confirm and extend the results with the addition of a lower dose group, was performed by the same laboratory investigators who conducted the first study (Deacon *et al.* 1981). Rats were exposed to MEK by inhalation at concentrations of 400, 1000, or 3000 ppm. Unlike the initial study, there were no gross or soft tissue malformations at any exposure level and no effects seen at 400 or 1000 ppm. A significant decrease in maternal body weight gain and water consumption was observed in the animals exposed to 3000 ppm MEK. The skeletal abnormalities seen in the previous study were not seen in this study. At the 3000 ppm exposure, there was no difference in malformation frequency, the number of fetuses/litter, fetal body weight, or crown-rump length. However, the researchers observed a significant increase in the incidence of delayed skeletal ossification and an increase in the incidence of extra lumbar ribs at this dose level. The authors concluded that MEK was not embryotoxic or teratogenic and only slightly fetotoxic in the rat at exposure concentrations of 3000 ppm. This study did not confirm the effects observed only at the 1000-ppm dose in the earlier study, and the occurrence of effects in only the low dose group of the previous study suggests those effects were not treatment-related. The maternal and developmental NOELs from this study were 1000 ppm.

To validate the conclusions from the Deacon *et al.* study and to determine effect/no-effect levels in non-pregnant females, a third study was conducted (Schwetz *et al.* 1991; Mast *et al.* 1989)

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<sup>57</sup> 68 Fed. Reg. 32606, 32613 (May 30, 2003).

<sup>58</sup> 63 Fed. Reg. 13185 (March 30, 1998).

and reported on the developmental effects of MEK in another species, Swiss mice. Groups of pregnant and nonpregnant mice were exposed to MEK vapor concentrations of 400, 1000, or 3000 ppm for 7 hr/day for 10 consecutive days. There were no differences in sensitivity to MEK exposure between the pregnant and nonpregnant mice. There were indications of maternal toxicity shown by concentration-related increases in relative liver and kidney weights, which were significant in the 3000 ppm dams. A mild decrease in fetal body weight was observed for both male and females at 3000 ppm; however, this was statistically significant only for males. There were no statistically significant increases in the number of malformed fetuses per litter, although there were several atypical malformations not often found in control litters. There was a significant finding of increased incidence of misaligned sternbrae, a skeletal variation, at 3000 ppm. No developmental or maternal effects were observed at vapor concentrations of 1000 ppm or less. After considering the results from the present study together with results obtained in rats, the authors concluded that MEK vapors caused developmental toxicity and a low incidence of malformations at concentrations that caused maternal toxicity (*i.e.*, 3000 ppm). No maternal or developmental toxicity was observed at concentrations of 1000 ppm MEK or below.

Thus, the two studies conducted subsequent to Schwetz *et al.* (1974) demonstrated that 1000 ppm is the NOAEL in both the rat and the mouse. The only consistent fetal effect was delayed ossification at the 3000 ppm level, in the presence of maternal toxicity. This is a developmental delay, typically overcome before weaning based on studies of other substances, and most likely secondary to the maternal toxicity. There was no reproducible evidence of selective developmental effects and the inability of the original investigators to reproduce their 1974 results, *i.e.*, developmental toxicity below maternally toxic levels, suggests these early results were anomalous. The IRIS Toxicological Review of Methyl Ethyl Ketone confirms a NOAEL of 1000 ppm for developmental toxicity in rats and mice (see p. 62, Table 5).

The results of the MEK studies are supported by a developmental toxicity study conducted with 2-butanol (Nelson *et al.* 1989). In that study, pregnant Sprague-Dawley rats were exposed by inhalation to 0, 3500, 5000, or 7000 ppm 2-butanol for 7 hours/day on gestation days 1-19. At concentrations of 5,000 and 7,000 ppm, the maternal rats exhibited narcosis and impaired gait during the exposure period, and the 7,000 ppm group did not fully recover by the next exposure day. Maternal body weight gain and food consumption were reduced at all exposure levels. Statistically increased incidences in resorptions/litter and decreases in live fetuses/litter were seen in the 7,000 ppm group. There were also significant reductions in fetal body weight at 5,000 and 7,000 ppm. This study demonstrates that 2-butanol is not teratogenic and is not developmentally toxic except at very high concentrations that produce significant maternal effects.

In another study relevant to this assessment (Gallo *et al.* 1977), sBA was administered to rats via drinking water as part of a combined reproductive and developmental study. In the developmental portion of the study, there were no effects at 1% in the drinking water (approximately 1500 mg/kg/day). At the 2% level (approximately 3000 mg/kg/day) there was slight maternal toxicity and significant fetal weight depression. The results of these studies are consistent with those of Deacon *et al.* (1981) and Schwetz *et al.* (1991) and support the view that MEK is not a selective developmental toxicant.

The 2-generation reproductive effects study on Wistar rats (described in Section 7.6) also included a teratologic phase in which the parent dams were rebred (2nd litters) and subjected to cesarean section on day 20 of gestation after being exposed to 2-butanol at 0, 0.3, 1.0 and 2% in drinking water (Cox *et al.* 1975). Pregnancy rates and survival of these females were

unaffected. The body weight of the pregnant dams was not depressed. Examination of uterine contents on the 20th day of gestation suggested that 2-butanol was somewhat fetotoxic at the 2% dosage level, as shown by the decreased mean pup weights. This response was minimal, however, as indicated by the lack of any effect on implantation or the occurrence of early or late fetal deaths. There were no significant soft tissue findings in the group treated at the 2% dosage level.

In summary, the developmental toxicity potential of MEK (or 2-butanol, a metabolic surrogate) has been studied in rats and mice by inhalation and in rats following oral exposure. In these studies, MEK produces some developmental toxicity, but not teratogenicity, at the highest dose examined. In most of these studies, the high dose effects were associated with maternal toxicity.

EPA has concluded that “the concern for developmental toxicity [from exposure to MEK] appears to be low,”<sup>59</sup> and the MEK SIAR concludes that MEK does “not appear to present significant risk of adverse . . . developmental effects.” (OECD 1997, p.3). Further developmental toxicity testing for MEK appears unnecessary at this time.

## 7.8 Immunotoxicity (Tier 2)

In the progressive and methodical development of the MEK database evaluating toxic risk, no further specific immunotoxicity studies have been initiated. The weight of evidence in the dermal irritation/sensitivity studies (including humans) and the multiple repeated-dose animal studies with MEK and/or 2-butanol indicates that these compounds are neither allergens nor immunosuppressants, and there is no need for further immunotoxicity testing. In fact, the assessment of clinical immunosuppression can be determined in the subchronic rodent studies by considering “... the relationship between changes in the structure and/or function of discrete components [lymph nodes, thymus, and spleen, via pathology and weights] of the immune system and holistic changes in the susceptibility to infectious or malignant disease.” (Karbe *et al.* 2002).

MEK was not a contact allergen in the mouse ear swelling test (Descotes 1988) and there was no evidence of MEK-induced skin sensitization of Hartley albino guinea pigs in a study where MEK was used as the vehicle control/solvent (Cannelongo *et al.* 1978). In measuring pulmonary sensitization, the MEK concentration necessary to produce a 50% decrease in the initial respiration rate (*i.e.*, the RD50) in mice was 10,745 ppm (DeCeaurriz *et al.* 1981). This high concentration indicates a lack of immediate allergenic sensitizing response. In humans, no sensitization reactions were seen in volunteers exposed to a 20% MEK in petrolatum mixture (Epstein 1975).

The stimulation of specific immune responses that might result in allergic disease can also be assessed by presence or absence of clinical signs such as contact dermatitis, allergic sensitization of respiratory tract (rhinitis and/or asthmatic breathing) and gastrointestinal disease in repeated-dose studies.

None of the above mentioned pathologic changes to lymphoid tissue or clinical observations were detected or noted for the repeated-dose MEK or 2-butanol studies. Therefore, a need does not exist to pursue “small changes in immunological function” to assess a health risk when there were no holistic changes in test animal susceptibility to infection or malignant disease.

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<sup>59</sup> 63 Fed. Reg. 15195 (March 30, 1998).

This conclusion is confirmed by a recent publication by E. Karbe, G.M. Williams, R.W. Lewis, I. Kimber, and P.M.D. Foster in the peer-reviewed journal, *Experimental Toxicologic Pathology*, (2002) Volume 54: 51-55, which discusses distinguishing between adverse and non-adverse effects in various tissues and biologic systems. They had this to say about the immune system:

“The adaptive immune system in vertebrates has evolved to *provide resistance to infectious microorganisms and malignant disease*. Effects can take one of two forms - immunotoxicity (immunosuppression) resulting in impaired immune function and reduced host resistance, or stimulation of the specific immune responses that result in allergic disease.”

“Parameters relating to immunotoxicity are changes in morphology of lymphoid tissue, the impairment of immunological function of various cell populations, the reduction of the concentration of lymphocyte subpopulations, and the decrease in host resistance realized in *in vitro* assays. It appears that various changes of above parameters may be induced without affecting host resistance. Obviously, a considerable functional reserve exists in the whole immune system. Thus, small changes in immune status can be tolerated without an increase in host susceptibility due to functional redundancy in the immune system and the existence of compensatory and complementary mechanisms.”

Additionally, an immunotoxicity study – using the test guideline specified in the VCCEP Pilot Announcement – of another ketone, acetone (also known as methyl methyl ketone), was recently conducted with no evidence of immunotoxic effects. (Woolhiser, *et al.* 2003.) CD-1 mice were exposed to 0, 600, 3000 or 6000 ppm acetone in drinking water for 28 days (equating to approximately 0, 100, 500 and 1000 mg/kg/day), and evaluated for anti-SRBC antibody response (including spleen weights and spleen cell counts), as well as hematology parameters and thymus weights. The absence of immunotoxic effects in this study of a structurally similar compound supports the belief that MEK is unlikely to be immunotoxic. A robust summary of this study is provided in Appendix B. (A full copy of the study will be provided upon request.)

Thus, weight of the evidence supports the conclusion that MEK does not cause adverse immunological effects, and further immunotoxicity testing of MEK is not necessary.

### **7.9 Carcinogenicity (Tier 3)**

MEK has not been tested specifically for carcinogenicity because data on its structure and metabolism, subchronic health effects, and genotoxicity indicate that MEK is not likely to have carcinogenic properties. MEK does not belong to a class of chemicals known to react with DNA nor is it metabolized to materials that are likely to react with DNA. Materials which are oncogenic for mammals appear to cause cancer either by interacting with the genetic material (DNA) (that is, they are genotoxic and, therefore, are probably initiators of the carcinogenic process), or they produce chronic toxic effects which result in increased cell turnover and, therefore, produce effects by epigenetic mechanisms and are probably promoters of the carcinogenic process. The data available for MEK indicate that it is not genotoxic and also does not produce significant cumulative toxicity. Therefore, MEK is unlikely to be carcinogenic by either genetic or epigenetic mechanisms and is unlikely to be either an inducer or promoter of carcinogenicity.

Although MEK has not been tested specifically for carcinogenicity, it has been used as a solvent for the investigation of the contribution of elemental sulfur and other organic sulfur compounds to dermal carcinogenesis in C3H male mice (Horton *et al.* 1965). No skin tumors were induced as a result of applying 50 mg of a 17% MEK solution to each mouse topically twice a week for one year.

Two studies have been conducted in workers exposed to MEK in dewaxing plants. Although the studies involved relatively small populations exposed to relatively low levels of MEK, each study reported that deaths due to cancer were less than would be expected in a normal population. In the first study, no overall excess in cancer incidence was found in a cohort of 446 males; 13 cancer deaths were observed compared to 14.26 expected (Alderson and Rattan 1980). An increase in cancer of the buccal cavity and pharynx was observed, based on very small numbers (2 observed compared to 0.13 expected). The overall cancer incidence also was less than would be expected in a normal population in a second study of 1,008 male oil refinery workers exposed to 1-4 ppm MEK in a dewaxing-lubricating oil plant (Wen *et al.* 1985). No increase in buccal and pharyngeal cancers was observed in this second study. ATSDR reviewed these studies and concluded that “preliminary epidemiological studies suggest that occupational exposure to [MEK] does not increase the development of neoplasms.” (ATSDR 1992 at p. 49).

The IRIS Toxicological Review of Methyl Ethyl Ketone (2003) concludes that “SAR [structure activity relationship] 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).” (p. 56; see also pp. 48-49). In its proposed delisting of MEK as a HAP, the Agency stated:

“MEK is unlikely to be carcinogenic based on the lack of any structural features or alerts indicative of carcinogenic potential as a result of mechanism-based structure-activity relationship (SAR) analysis (Woo *et al.* 2002). Further, Woo has given MEK a low concern rating (unlikely to be of cancer concern) based on comparison to acetone for which there is no evidence of carcinogenicity, and the fact that there is no evidence that unsubstituted mono-ketones have been associated with carcinogenicity/ genotoxicity. There is also no reason to anticipate any electrophilic reactivity for unsubstituted mono-ketones mentioned above (*i.e.*, no structural alerts). . . . Methyl ethyl ketone has been tested for activity in an extensive spectrum of *in vitro* and *in vivo* genotoxicity assays and has shown no evidence of genotoxicity in most conventional assays. . . . Overall, studies of MEK yield little or no evidence of genotoxicity. . . . Based on these results, we believe that MEK may not reasonably be anticipated to be carcinogenic.”<sup>60</sup>

The MEK SIAR similarly concludes, “MEK is not genotoxic and is not likely to be carcinogenic.” (OECD 1997, p.3). Accordingly, carcinogenicity testing of MEK is not necessary.

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<sup>60</sup> 68 Fed. Reg. 32606, 32613 (May 30, 2003).

### 7.10 Neurotoxicity (Tier 3)

Numerous studies have been conducted to assess the neurotoxic potential of MEK. None of the studies provides any evidence that MEK produces nervous system damage. The IRIS Toxicological Review of Methyl Ethyl Ketone (2003) concludes, "Several well-conducted studies in experimental animals . . . provide no convincing evidence that repeated exposure to MEK, by itself, is capable of producing persistent neurological effects." (p. 54). Similarly, the IRIS Summary states, "Animal studies provide no convincing evidence that exposure to MEK alone causes persistent neurotoxic effects." (p. 13)

In the series of human studies by Dick *et al.* (1984, 1988/1989, 1992), no significant differences between the exposed and control populations were observed for any of the neurobehavioral parameters. The studies included five psychomotor tests: choice reaction time, simple reaction time, visual vigilance, dual task (auditory tone discrimination and tracking), and memory scanning. One sensorimotor test (postural sway) also was included. The IRIS Toxicological Review of Methyl Ethyl Ketone states (p. 17): "In an extensive series of studies involving 4-hour exposure of human subjects to 200 ppm (590 mg/m<sup>3</sup>) MEK, National Institute for Occupational Safety and Health (NIOSH) investigators found no statistically significant increase in reported symptoms of throat irritation, nor did they find marked performance changes in a series of tests of psychomotor abilities, postural sway, and moods (Dick *et al.* 1984, 1988, 1989, 1992)."

Egan *et al.* (1980) exposed male rats 22 hours per day for 180 days to 500 ppm MEK via inhalation. There were no clinical signs of neurological effects. Histopathological examination of the lumbar cord, dorsal and ventral spinal roots, spinal ganglia, sciatic notch and tibial nerve showed no evidence of neurological effects.

Saida *et al.* (1976) evaluated the effects of MEK alone and in combination with methyl-n-butyl ketone (MnBK) in Sprague-Dawley rats. Animals were exposed continuously (*i.e.*, 24 hours/day) to MEK at 1,125 ppm; to a mixture of MnBK and MEK that consisted of MnBK at 225 ppm and MEK at 1,125 ppm; or to MnBK at 225 ppm. Rats were sacrificed 16, 25, 35, and 55 days after initiation of treatment. Nerve tissue was collected for microscopic examination, and quantitative histological studies were performed. No peripheral neurotoxicity was seen with MEK alone. In addition, it was reported that further studies were carried out for as long as 5 months without evidence of abnormality. The combination of MnBK and MEK was more toxic than MnBK alone as measured by onset to clinical paralysis and by several histological parameters.

A study by Spencer *et al.* (1976) evaluated the neurotoxic potential of MEK alone and in combination with MnBK and methyl isobutyl ketone (MIBK) in cats. Test materials were administered by subcutaneous injection twice daily, 5 days per week for up to 8.5 months. Selected tissues were removed and examined by light and electron microscopy. Chronic intoxication with commercial grade MEK alone produced no clinical or pathological evidence of neuropathy. Animals treated with a 9:1 mixture of commercial grades of MEK and MnBK failed to develop clinical neuropathy, although pathological evidence of nerve damage was present. The subclinical damage appeared to be in proportion to the amount of MnBK used, although enhancement by MEK of the neurotoxic effects of MnBK could not be excluded.

A study by Altenkirch *et al.* (1978) evaluated the neurotoxic potential of MEK alone and in combination with n-hexane. Rats were exposed 8 hours/day, 7 days/week for 15 weeks. MEK was initially present at 10,000 ppm, but this level was reduced to 6,000 ppm after several days because of severe irritation to the upper respiratory tract. As in the other studies, the animals

were sacrificed and perfused, and sections of nerve tissue were examined microscopically. Rats exposed to MEK did not develop any obvious motor impairment up to the seventh week when all animals died without neurological symptoms. Histopathological examinations revealed severe signs of bronchopneumonia in all animals. There was no evidence of histological alterations in the nerve tissue. Thus, MEK was found to be without neurotoxic potential. However, there was some evidence that MEK potentiated the neurotoxic effects of n-hexane.

The study by Cavender *et al.* (1983), described in Section 7.5 (subchronic studies), provides further evidence that repeated inhalation exposures (at doses up to 5,000 ppm) produce no clinical or pathological evidence of neurotoxic effects in rats. No histopathological lesions were reported in the brain, sciatic nerve, tibial nerve, spinal cord, or optic nerves, nor were any effects reported in posture, gait, tone, or symmetry of the facial muscles, or in the pupillary, palpebral, extensor thrust, and cross-extensor thrust reflexes. A slight but statistically significant increase in brain weight was reported in female rats exposed to 5,000 ppm, but no pathological changes were reported in the medulla oblongata or the sciatic and tibial nerves. Based on the Cavender study, ECETOC concluded that the neurotoxicity NOAEL in rats for MEK is 5,000 ppm (ECETOC 1996). Thus, the earlier observation by Saida *et al.* (1976) that MEK was not neurotoxic in rats, even following repeated exposure at relatively high levels, was confirmed.

The IRIS Toxicological Review of MEK (2003) states, "Neurotoxicity is adequately addressed by the subchronic inhalation study of Cavender *et al.* (1983), in which animals were examined for both neurological function and for central nervous system lesions with special neuropathological procedures. The results from this study indicate that MEK has little, if any, neurotoxic potential by itself when tested in adult laboratory animals under conditions of high-level repeated inhalation exposure." (p. 82).

The effect of MEK exposure on neurophysiology also was evaluated by Takeuchi *et al.* (1983). Rats were exposed 12 hours a day for 24 weeks to 200 ppm MEK vapor. The rats showed significant increases in motor nerve conduction velocity and mixed nerve conduction velocity and reduced distal motor latency after four weeks of exposure. However, significant effects were not observed at any other times. The biological significance of these findings is doubtful. The effects were transitory in nature, and in other studies there was no evidence of behavioral changes or microscopic damage to nerve tissue at much higher exposure levels or following exposure for longer periods of time. The alteration in nerve conduction velocity at four weeks also was not corroborated by histopathology and was in the opposite direction to that predicted by peripheral neurotoxins such as n-hexane. The IRIS database summary for MEK concludes that Takeuchi *et al.* "found no evidence of a persistent effect on motor or mixed nerve conduction velocity, distal motor nerve latency, or histopathological lesions of tail nerves." p. 14/23. (p. 14)

It has been recognized in the scientific literature that alkanes and ketones that can be metabolized to gamma-diketones are neurotoxic, while those that cannot be metabolized to the gamma-diketones are not neurotoxic (DiVincenzo *et al.* 1976; Krasavage *et al.* 1977; Spencer *et al.* 1976, 1985). The gamma-diketones react with primary amino functions of proteins to form pyrrolyl adducts, that then undergo oxidation to electrophiles that react with protein nucleophiles to result in protein cross-linking. Cross-linking of neurofilaments is widely recognized as the mechanism underlying the formation of neurofilament-filled axonal swellings that characterize this neuropathy. (Graham *et al.* 1984). As EPA recognized in its IRIS Toxicological Review (2003), because MEK is not metabolized to gamma-diketones, exposure to MEK would not be expected to produce peripheral neurotoxicity (p. 57). (See also O'Donoghue *et al.* 1984; Topping *et al.* 1994).

One cross-sectional health study of workers in three Romanian factories purported to show neurotoxic effects from exposure to MEK (Mitran *et al.* 1997, 2000). EPA has concluded that the Mitran study has numerous weaknesses that render it unsuitable for drawing any conclusions about the neurotoxicity of MEK. (IRIS Toxicological Review, pp. 21-22). EPA also evaluated the Mitran study in connection with its review of the petition to remove MEK from the HAP list, and stated as follows:

“The EPA’s National Center for Environmental Assessment (NCEA) and National Health and Environmental Effects Research Laboratory (NHEERL) reviewed the referenced study as part of our technical review. Their review demonstrated that the study has multiple and serious methodological shortcomings that greatly reduce its meaningfulness. Very few methodological details were presented in the study, making it virtually impossible for EPA reviewers to determine what had been done. . . . Importantly, the study did not address the control of temperature, a critical factor in nerve conduction studies, and the pattern of nerve conduction results is not entirely consistent with the reported peripheral neuropathy. Of primary importance in EPA’s review was the consideration of the extent to which the study’s findings are supported by the existing scientific literature. In this regard, we conclude that the study cited in the comment is inconsistent with a large volume of high quality neurotoxicological scientific evidence. In fact, animal models of the reported condition are excellent predictors of human neuropathy. MEK has been well tested for the reported condition and is convincingly negative.”<sup>61</sup>

In summary, studies show that MEK has essentially no neurotoxic potential. Further neurotoxicity testing of MEK appears unnecessary at this time.

### **7.11 Developmental Neurotoxicity (Tier 3)**

MEK has not been the subject of a separate developmental neurotoxicity study. The totality of scientific evidence available for MEK is not suggestive of a likely developmental neurotoxicity hazard. As discussed in Sections 7.7 and 7.10, above, tissue examination of fetuses in multiple guideline-quality developmental toxicity studies showed no indication of a primary effect on the nervous system. (Schwetz *et al.* 1991; Deacon *et al.* 1981; Schwetz *et al.* 1974.) Clinical/behavioral observations in long-term (3-6 months) rodent studies and human exposure studies showed no concern for neurotoxicity. Extensive neuropathologic investigation in rodents did not reveal any lesions that could be attributed to MEK exposure and human behavioral performance tests also showed no neurological dysfunction and no significant neurological effects. (Egan *et al.* 1980; Cavender *et al.* 1983; Dick *et al.* 1984, 1988/89, 1992.) Extensive neuropathology was performed on the 90-Day and 6-Month Repeated-dose animals that were also clinically asymptotic.

In sum, the MEK developmental toxicity studies show no evidence of neurological effects on offspring, while both animal and human neurotoxicity studies provide no evidence that MEK is neurotoxic. The current IRIS database recognizes that MEK, by itself, has little if any neurotoxic

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<sup>61</sup> 68 Fed. Reg. 32606, 32618 (May 30, 2003).

potential. See related discussion in Section 7.10 -- Neurotoxicity. In light of the available evidence, no further developmental neurotoxicity testing appears warranted at this time.

## 7.12 Human Data

Several studies have been conducted to evaluate potential toxicity of MEK to humans. In some cases humans were exposed under laboratory conditions, whereas other studies involved assessments of effects of occupational exposure.

Dick *et al.* (1984, 1988/1989, 1992) tested the neurobehavioral potential of exposure to 200 ppm MEK for 4 hours in humans.<sup>62</sup> Over 100 men and women were examined in this study and a large number of neurobehavioral parameters were reviewed. The study also evaluated the following “subjective effects”: odor presence, strong odor, objectionable odor, headache, nausea, throat irritation, tearing and unpleasant odor. The results showed no statistically significant increase in any subjective effects between subjects exposed to 200 ppm MEK for 4 hours and controls, except for a finding of “strong odor.” (Dick *et al.* 1992). Muttray *et al.* (2002) exposed 19 male volunteers to 200 ppm for 4 hours and also did not find evidence of irritation (based on a questionnaire).

In an earlier study by Nelson *et al.* (1943), human volunteers were exposed for three to five minutes to differing vapor concentrations. MEK reportedly produced “slight” nose and throat irritation at 100 ppm in an unspecified number of subjects. Mild eye irritation was reported by some subjects at 200 ppm, but the majority of test subjects concluded that 200 ppm MEK would be tolerable for an 8-hour work day. Exposure to 300 ppm was considered objectionable. Based on these observations, the authors recommended a maximum occupational exposure level of 200 ppm. The reports of “slight” and “mild” irritation in the Nelson study should be interpreted with caution as they likely overstate MEK’s potential to cause irritation, based on the more recent and robust studies by NIOSH. Nelson *et al.* used few test subjects, and the short duration of exposure makes it difficult to determine whether the subjective responses reflected odor perception or true sensory irritation.<sup>63</sup> It is well known that odor can influence subjective responses to chemical exposures (Cavallini *et al.* 1991; Knasko *et al.* 1990).

Elkins (1959) reported an investigation of industrial exposure to MEK prior to 1950. In certain processes in Massachusetts, exposures reportedly were as high as 700 ppm. Concentrations above 300 ppm reportedly resulted in complaints of headaches and throat irritation, and, in one plant, nausea and vomiting were reported with concentrations reportedly averaging 500 ppm. However, no permanent effects were noted. The study by Elkins also needs to be interpreted with caution because of the reliance on subjective complaints and incomplete information about peak exposures, exposures to other compounds and other aspects of the work conditions.

OSHA has established a permissible exposure limit (8-hour TWA) for MEK of 200 ppm. ACGIH recommends an 8-hour threshold limit value (TLV) of 200 ppm and a 15-minute short-term exposure limit (STEL) of 300 ppm.

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<sup>62</sup> This series of studies is discussed further in Section 7.10 (Neurotoxicity).

<sup>63</sup> Nelson *et al.*, (1943) lacked analytical determination of MEK concentrations in their study of acetone irritancy and should be judged unreliable for use (Klimisch rating 3b: “significant methodological deficiencies”).

### 7.13 Selection of Health Benchmarks

The relevant health benchmarks for this risk assessment are the IRIS inhalation RfC of 5.0 mg/m<sup>3</sup> and oral RfD of 0.6 mg/kg/day, previously described in Section 3.1. These values represent daily exposures that EPA estimates may be continued for a lifetime for the general population, including sensitive subgroups, without appreciable risk of adverse effects (EPA 1994).

In the case of the RfC, NCEA initially proposed a value of 15.0 mg/m<sup>3</sup>, based on total uncertainty factors of 100, including a database UF of 3.<sup>64</sup> External peer reviewers expressly approved of the proposed uncertainty factors,<sup>65</sup> but during Agency consensus review NCEA increased the database deficiency UF to 10. The discussion of this UF in the final IRIS documentation understates the available data by not recognizing the relevance of the oral reproduction study of sBA used to derive the RfD, and failing to mention the extensive histopathology of reproductive organs in the subchronic study by Cavender *et al.* (the utility of this information is recognized elsewhere in the document). In addition, MEK used a duration adjustment even though MEK is rapidly absorbed, distributed, and metabolized, such that peak exposure levels are likely to be more important than AUC for predicting developmental toxicity. The duration adjustment by EPA lowered the RfC by an additional factor of 3.5. The Panel believes the proposed RfC of 15.0 mg/m<sup>3</sup> was fully protective of human health. A copy of the Panel's comments on EPA's Draft IRIS Update and Toxicological Review of MEK is provided at Appendix F.

Swartout *et al.* (1998) have demonstrated that the approach used to set most RfDs and RfCs (use of animals models and safety factors) is conservative for the vast majority of chemicals, such that these health benchmarks are best viewed as the lower bound of the true but unknown "safe level". They further demonstrated that the true threshold for adverse effects for the "typical" chemical could be 10 to 100 times higher than the RfD or RfC. This finding does not prevent the use of these values in screening assessments. Since the RfD or RfC is, by design, intended to be a conservative measure of the "safe level", in this case based on total uncertainty factors of 1000 for the RfD and 300 for the RfC, a comparison to these values is still a valid tool for screening out chemical exposures that are of low concern.

### 7.14 Other Information

#### Potential of Toxicity of Other Compounds

High acute exposures to MEK have been shown to potentiate the effects of several other compounds, including MnBK (Saida *et al.* 1976), n-hexane (Altenkirch *et al.* 1978), and 2,5-hexanedione (Ralston *et al.* 1985). As EPA concludes in the IRIS Toxicological Review, "[T]he potentiating effects of MEK on the toxicity of other solvents have only been demonstrated at relatively high [MEK] exposure concentrations." (p. 58). These mixed exposure scenarios are beyond the scope of this assessment. Additional information about potentiation may be found in the previous assessments described in Section 3.

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<sup>64</sup> Draft IRIS Toxicological Review of Methyl Ethyl Ketone (March 2003), pp. 69-70.

<sup>65</sup> Final IRIS Toxicological Review of Methyl Ethyl Ketone, Appendix A, p. A-9.

## 7.15 Hazard Summary

As described in this Hazard Assessment and previous regulatory and peer-reviewed assessments of MEK toxicology data, the toxicological effects of MEK have been well studied, and MEK has low acute and chronic toxicity. The key health benchmarks for this risk assessment are the inhalation reference concentration of 5.0 mg/m<sup>3</sup> and oral reference dose of 0.6 mg/kg/day posted by EPA on the IRIS database. These values, as a matter of EPA policy, are intended to represent exposures that may be continued for a lifetime for the general population, including sensitive subgroups, without appreciable risk of adverse effects. The following paragraphs address in summary fashion each toxicity endpoint covered by the VCCEP.

**Acute Toxicity:** MEK has a low order of toxicity following single oral exposure in rodents. The LD<sub>50</sub> in adult rats is 6.86 mg/kg (5.59 - 8.45 range).

**Mutagenicity:** MEK has been tested in a wide battery of mutagenic assays and the weight of the evidence from these assays is that MEK is not mutagenic.

**Systemic (Repeated Dose) Toxicity:** MEK showed a low order of toxicity in subchronic studies, producing no observable toxic effects at doses up to 5000 ppm in a 90-Day inhalation toxicity study. Histopathological studies included extensive examination of reproductive organs. None of the examined tissues (testes, epididymides, seminal vesicles, vagina, cervix, uterus, oviducts, and ovaries) showed lesions attributed to MEK exposure.

**Developmental and Reproductive Toxicity:** MEK was not teratogenic in 2 rat and 1 mouse Prenatal Developmental Toxicity studies (pup NOAELs/NOEL ranged from 1000 - 3500 ppm) or in a rat sBA Prenatal Developmental Toxicity study where the pup NOEL was 1771 mg/kg/day (dosed through total gestation period). sBA (direct metabolic precursor for MEK) was not considered a reproductive hazard in a 2-Generation Reproductive Toxicity study in rats. The maternal and pup NOAELs were 1771 mg/kg/day.

**Immunotoxicity:** MEK is not likely to be an immunotoxicant. MEK exposure of vapors at 5000 ppm for 6 hr/day, 5 days/week in a subchronic study showed no indication that immune enhancement or immune suppression takes place. Likewise, in the sBA 2-Generation Reproductive Toxicity study at a dosage of 1771 mg/kg/day there were no indications of immune system modulation. A structurally similar compounds, acetone, was evaluated in a 28-day guideline immunotoxicity study in CD-1 mice and did not produce any immunotoxic effects.

**Metabolism and Pharmacokinetics:** MEK pharmacokinetics and metabolism have been well studied. MEK absorption is rapid via all routes, and clearance of MEK and its metabolites in mammals is essentially complete in 24 hours. The bulk of MEK taken into the mammalian body enters the general metabolism and/or is eliminated as simple compounds such as carbon dioxide and water.

**Carcinogenicity:** MEK is not considered potentially carcinogenic given lack of genotoxic potential and low order of repeated dose toxicity. As EPA has concluded, "MEK is unlikely to be carcinogenic based on the lack of any structural features or alerts indicative of carcinogenic potential as a result of mechanism-based structure-activity relationship (SAR) analysis (Woo *et al.* 2002). Further, Woo has given MEK a low concern rating (unlikely to be of cancer concern) based on comparison to acetone for which there is no evidence of carcinogenicity, and the fact

that there is no evidence that unsubstituted mono-ketones have been associated with carcinogenicity/ genotoxicity.” 68 Fed. Reg. 32606, 32613 (May 30, 2003).

**Neurotoxicity and Developmental Neurotoxicity:** High acute exposure to MEK can cause reversible pharmacologic effects, but available studies do not provide any evidence of injury to the nervous system following repeated exposures. Extensive neuropathology was performed on the 90-day and 6-month repeated-dose animals that were also clinically asymptotic. The IRIS Toxicological Review of Methyl Ethyl Ketone (2003) concludes, “Several well-conducted studies in experimental animals . . . provide no convincing evidence that repeated exposure to MEK, by itself, is capable of producing persistent neurological effects.” (p. 54) Similarly, the IRIS Summary states, “Animal studies provide no convincing evidence that exposure to MEK alone causes persistent neurotoxic effects.” (p. 13)

Developmental neurotoxicity has been indirectly evaluated via the tissue examination of fetuses in multiple guideline-quality developmental toxicity studies (3 MEK and 2 sBA) and evaluation of the newborn pups in the 2-generation reproduction developmental toxicity study (sBA). The results showed no indication of a primary effect on the nervous system.

#### **7.16 Robust Summaries of Toxicology Studies**

The OECD SIDS Dossier and SIAR (Appendix A) contain summaries of most of the key toxicological studies of MEK. Twenty-two expanded robust summaries supporting this VCCEP document are found in Appendix B.

## 8. Exposure Assessment

### 8.1 Introduction

This section presents the results of a child-specific exposure assessment for MEK. MEK was included in the VCCEP program partly because of its detection in blood samples in the NHANES adult biomonitoring program. MEK is a naturally occurring human metabolite, is present naturally in foods across all food groups, and is produced by microbes, algae, plants and other organisms. It is also released to the environment via anthropogenic production, where it primarily partitions to air. Its primary use is industrial, but it can also be found in consumer products, especially coatings and adhesives, and has minor use in the food industry as an extraction agent and flavoring agent.

The only exposure pathway identified unique to children was breast milk. None of the consumer products that contain MEK are targeted specifically towards children, with the exception of hobby model paints and adhesives, which are targeted towards older children and adults. Due to age-specific behavior or physiology, for a given exposure source children may have differential potential exposure than adults. Child exposure was estimated for all plausible pathways. Adult exposure was considered as relevant for children, including potential for transfer via physical contact and breast milk for nursing infants.

These results indicate that on a chronic basis, natural occurrence in food is likely the main exposure pathway in the general population of children. Ambient media concentrations (air, water, and soil) are generally low, even in source dominated areas. Indoor uses of consumer products can result in higher acute exposures, but these are short-lived and MEK is rapidly metabolized and excreted (thus acute exposures do not lead to an increase in body burden over time).

### 8.2 Overview of Approach

Information on all sources (natural and anthropogenic) of MEK, media concentrations, and physical-chemical properties were gathered and summarized. All pathways potentially relevant to children's exposure were considered, including child contact with environmental media (indoor and outdoor air, surface water, soil), food, drinking water, potential for parental transfer to child (breast milk or dermal contact), direct consumer product use or presence during consumer product use, and other sources. A tiered approach to exposure assessment was used, based upon screening level, conservative techniques with refinement as indicated. Pathways considered are presented below (and in Table 8.1).

- Ambient Media:
  - Outdoor Air - typical and source dominated areas
  - Indoor Air - typical or indoor sources - residential, school and car
  - Soil
  - Food - natural occurrence
  - Breast Milk - background and from occupationally exposed mother
  - Water
- Specific Sources:
  - Consumer Product Use (inhalation and dermal)
  - Food- Flavoring, food industry use
  - Other Sources (building materials, pharmaceuticals)

**Table 8.1 General Matrix of Exposure Sources Considered**

Exposure Route	CHILD'S ENVIRONMENT			
	CAR	RESIDENCE	COMMUNITY/ INDUSTRIAL	SCHOOL/ DAYCARE
Inhalation	New car - off-gassing from use in construction materials	<u>Background:</u> Ambient (outdoor) air (urban and rural) Residential indoor air  <u>Possible residential sources:</u> New home Consumer product home use	Source: Facility releases	Background  Consider if there are any specific sources unique or differentially used in schools
Dermal	Inhalation is the most relevant pathway	<u>Sources:</u> Consumer products Soil unlikely as per physicochemical (p-chem) properties	Soil unlikely as per p-chem properties	Consider if there are any specific sources unique or differentially used in schools
Ingestion		a) Food: Background: Natural levels Source: Flavoring use b) Water: Background: Measured levels Any sources, <i>i.e.</i> , consumer products c) Breast milk: - Background - natural occurrence d) Soil unlikely as per p-chem properties	Breast Milk: Potential from maternal occupational exposure	No unique sources expected in schools

### 8.3 Sources of MEK

#### 8.3.1 Occurrence in Nature

##### Natural metabolite in humans.

MEK is a metabolic by-product of isoleucine catabolism in humans (Scriver *et al.* 2001). MEK is a metabolite of acetoacetyl-CoA, and a precursor of propionate. MEK accumulation in urine and blood has been observed in humans with metabolic deficiencies in isoleucine catabolism. Blood and urine levels, representative of typical or elevated conditions, were not provided in Scriver *et al.* (2001). Due to its volatility, routine methods for urinalysis make it difficult to quantify, and a typical quantitative profile is not available for urine. Further searching of medical references (Medline Plus) indicated that common blood diagnostics typically measure total ketone bodies rather than specific compounds.

##### 8.3.1.1 Production by bacteria, algae, plants, insects

MEK is a natural product emitted by some trees and found in some fruits and vegetables (see also section on natural occurrence in food) (HSDB 2001; ATSDR 1992). It is emitted by European firs, cedars, cypress trees and ferns, and has been detected in mulberry leaves (Tsao and Pfeiffer 1957). It is also emitted in ant secretions. It has been detected in the scent storage sac of the green vegetable stinkbug (Forney and Markovetz 1971). It is a natural metabolic byproduct of plants and animals (HSDB 2001). It is detected in various species of microalgae at

concentrations as high as 2.6 ppb (ATSDR 1992). It is produced in landfills via microbial breakdown processes.

### 8.3.1.2 Release via volcanic emissions and combustion.

MEK is released into air via volcanoes and forest fires (HSDB 2001).

### 8.3.1.3 Natural Occurrence in Food

MEK is present as a natural constituent of many food products, in all food groups (fruits and vegetables, dairy, meat, and grains). In addition, sec-butanol also occurs naturally in many food items. Sec-butanol is rapidly metabolized into MEK in humans, and consumption of foods containing sec-butanol could contribute to plasma levels of MEK.

The Volatile Compounds in Food (VCF) database reports natural occurrence of volatile compounds in food items. It lists numerous references that report the natural presence of MEK in 127 food items (VCF 2000- Appendix G1). In many cases, MEK was detected but not quantified. Substances for which it was quantified, and measured values, are reported in Table 8.2. The VCF database also contains 210 articles on the natural occurrence of sec-butanol in foods (email from I. Nijssen dated 2/6/03).

**Table 8.2 - Quantified Items from VCF 2000**

<b>Food Item</b>	<b>Concentration ppm</b>
Apple juice	0.05 - 0.2
Beans (raw)	0.04
Black currants - berries	0.02
Butter	0.16
Cabbage (cooked)	0.05
Carrot	0.01-0.03
Cheddar cheese	0.01 - 67.1
Domati cheese	0.04 - 0.17
Chicken (cooked)	0.001
Cream	0.15 - 0.18
Egg (boiled)	0.003 - 0.009
Fish, lean (raw)	0.06
Guava fruit	0.0045
Lingonberry, cowberry	0.006
Milk	0.002 - 0.08
Peanut (raw)	0.004 - 0.01
Peanut (roasted)	0.1
Pear	0.7 - 1
Peas	0.03
Potato chips (American)	<0.01 - 0.13
Swiss cheese	0.1 - 0.7
Tea, microbial fermented	1
Tea, partially fermented	0.2 - 8
Tomato	3 - 6
Yogurt	0 - 7

A literature review of natural occurrence of MEK in food was also performed, and results are found in Appendix G2, Table G2-1. MEK has a minor use as a food flavorant (Section 8.8.1). In many cases, original literature was consulted to confirm that results cited in secondary sources were representative of natural occurrence, and concentrations provided were expressed on a food basis (rather than volatile constituents). The VCF database only includes information on natural occurrence in food. Sec-butanol occurrence in food is only from natural sources; some additional references on sec-butanol occurrence in food are found in Table G2-2, Appendix G2.

MEK has been shown to increase in some foods during aging (spoilage) (Appendix G2), consistent with the capability for bacterial production. MEK has been measured in the highest concentrations in foods where microbial activity is deliberately enhanced (cheese, yogurt).

Because MEK is not quantified in many food items in which it has been detected, it is difficult to provide a quantitative estimate of total child exposure via ingestion due to natural sources. In addition, even for the categories with concentration data, there is insufficient information to develop a distribution of MEK concentrations. To better characterize the potential range of child exposures from natural occurrence in food, ingestion ranges were estimated based upon four food items that children consume at a greater rate than adults consume. A screening level assessment of total potential children's intake was also performed. Details of these assessments are presented in Appendix G3.

One day doses were based upon intake rates for consumers only, whereas annual average daily doses are based upon per capita intake rates, which are more appropriate for average dose estimates for the general population (USEPA 1997a). Food ingestion data are typically based upon short term surveys (1-3 days). Per capita intake rates are generated by averaging consumer-only intakes over the entire population of consumers and non-consumers. In general, per capita intake rates are considered more appropriate for estimating average doses for the general population because they represent both individuals who ate the foods during the survey period and individuals who did not consume the foods during the survey period and individuals who did not consume the foods during the survey period but may eat them at some time (USEPA 1997a). Food concentrations were taken from the data in Appendices G1 and G2. Intake rates for specific items were taken from the USDA Continuing Survey of Food Intake by Individuals (USDA 1999). Intake rates by broad food category were taken from Table 3-35, USEPA 2002b.

The four specific food items evaluated were cheese, yogurt, apple juice, and milk. For these four items combined, estimated potential one-day intake of MEK ranges from 0.0005 - 1.16 mg/day and estimated annual average daily intake ranges from 0.001-0.42 mg/day (Table 8.3). In comparison, a general population estimate of 1.6 mg/day is presented in the Environmental Health Criteria (EHC) document (WHO 1992). In the EHC analysis, MEK intake was estimated as measured MEK concentration in select food items multiplied by the US annual consumption of these food items, and divided by a US population of 230 million. The food items used in the EHC analysis included: apple juice, white bread, butter, carrots, cheddar cheese, swiss cheese, fish, potato chips, tomatoes and yogurt.

The screening level assessment of total potential children's intake was consistent with the WHO general population estimate (screening level assessment details in Appendix G3). As a first step, children's food intake for the broad categories of dairy, grains, vegetables, fruit, fats, meat, egg and fish was used with the maximum and minimum concentrations reported for items within each category. This yielded a very high overestimate of consumption, as cheese concentrations were driving the maximum value in the dairy category. For a more realistic

assessment, the dairy category was further split into three subcategories: milk and milk drinks, yogurt, and cheese. The results of this analysis are also found in Table 8.3. Annual daily average intake is predicted to range from 0.003-6.1 mg/day, and one-day daily intakes from 0.006 - 8.6 mg/day. These values are only screening level, and highly uncertain given the incomplete information on MEK concentrations in individual food items within a category. However, they are consistent with the WHO estimate which was based upon a limited number of food items, and also not unreasonable when compared to the estimates for the 4 specific food items, considering the natural occurrence of MEK in multiple food sources. Nuts, tea and alcoholic beverages were not included in this current screening level assessment (as they were not included in the intake data for the broad food categories used in the assessment), and if ingested, they may also contribute to MEK intake based upon its natural presence in these items. Sec-butanol consumption was not included in this assessment.

**Table 8.3 Ranges of Estimated MEK Ingestion From Natural Occurrence in Food by Child Age**

<b>Combined cheese, yogurt, apple juice, milk:</b>					
<b>Age (yrs)</b>	<b>&lt;1</b>	<b>1-2</b>	<b>3-5</b>	<b>6-11</b>	<b>12-19</b>
<b>Intake (mg/day)</b>					
One-day intake	0.003 - 0.11	0.008 - 0.81	0.007 - 0.99	0.004 - 0.94	0.004 - 1.16
Annual average daily intake	0.001 - 0.007	0.002 - 0.25	0.002 - 0.34	0.001 - 0.30	0.001 - 0.42
<b>Dose (mg/kg/day)</b>					
One-day dose	0.00045 - 0.016	0.00068 - 0.066	0.00038 - 0.056	0.00013 - 0.031	0.00006 - 0.02
Annual average daily dose	0.00007 - 0.001	0.00019 - 0.02	0.0001 - 0.02	0.00003 - 0.01	0.00002 - 0.007
<b>For all food categories:</b>					
<b>Age yrs</b>	<b>&lt;1</b>	<b>1-2</b>	<b>3-5</b>	<b>6-11</b>	<b>12-19</b>
<b>Intake (mg/day)</b>					
One day intake	0.006 - 2.62	0.010 - 7.4	0.01 - 6.7	0.015-7.4	0.02 - 8.6
Annual average daily intake	0.003 - 0.98	0.006 - 3.4	0.007 - 4.0	0.009 - 4.8	0.013 - 6.1
<b>Dose (mg/kg/day)</b>					
One-day dose	0.0009 - 0.36	0.0008 - 0.61	0.0007 - 0.39	0.0005 - 0.24	0.0003 - 0.14
Annual average daily dose	0.0004 - 0.14	0.0005 - 0.28	0.0004 - 0.23	0.0003 - 0.16	0.0002 - 0.1

### 8.3.2 Anthropogenic Sources

#### 8.3.2.1 Overview of Production and Use Categories

Annual US production of MEK was 260,000 metric tons in 1999 (Section 5.2). MEK may be released to the environment by industrial facilities during manufacture or subsequent industrial application. It may also be released during use of consumer products that contain MEK. Major use categories of MEK are found in Table 8.4. These categories are discussed in more detail in Section 8.7 of this report, which identifies specific types of consumer products that may contain MEK.

**Table 8.4. MEK- Major Use Categories - Chemical Economics Handbook, SRI International 2000**

<b>Category</b>	<b>% of Total Production</b>
Coatings Solvents	55
Adhesives	12
Chemical Intermediate	6
Lube Oil Dewaxing	6
Magnetic Tapes	5
Printing Inks	4
Miscellaneous	12
TOTAL	100%

### **8.3.2.2 Other sources**

MEK may be produced in composting facilities and landfills via microbial degradation (HSDB 2001). It is also a combustion product, found in automobile, diesel, and jet aircraft exhaust.

MEK is also found in cigarette smoke (WHO 1992). Harmful effects of cigarette smoke in general are well recognized, including its association with various health impacts including but not limited to lung cancer, emphysema, chronic bronchitis, heart disease and stroke, none of which are related to the health hazards identified for MEK. MEK exposure via this source is not addressed further.

## **8.4 Physical-Chemical Properties and Environmental Partitioning**

Physical chemical properties of MEK are presented in Table 5.3.1. MEK is expected to exist solely as a vapor in the ambient atmosphere, based upon its vapor pressure (HSDB 2001). MEK is soluble in water but will evaporate from water surfaces based upon a Henry's Law constant of  $4.7 \times 10^{-5} \text{ atm}\cdot\text{m}^3/\text{mol}$  at 25°C (HSDB 2001). Volatilization is expected to be rapid, with an estimated river half-life of 15 hours (ATSDR 1992). MEK will volatilize from both dry and wet soils, based upon its vapor pressure and Henry's law constant, respectively.

MEK is biodegraded in the environment under both aerobic and anaerobic conditions (HSDB 2001). It is not expected to sorb in sediment or suspended matter or soil, based upon a log octanol-water partition coefficient of 0.29. These properties indicate that MEK is not persistent, and potential for bioconcentration via the food chain is not an issue.

In addition, these properties indicate that under environmental conditions, air and water are potential pathways for MEK exposure, but soil is not likely to be a significant pathway.

## **8.5 Ambient Levels in the Environment**

### **8.5.1 Measured Environmental Concentrations**

The studies below represent values for environments where a point source is not indicated to be present, to provide an assessment of typical "background concentrations" of MEK from all sources in the environment. Specific outdoor (facility) and indoor (consumer product) point sources are addressed in subsequent sections of this document.

Information was available in the public literature on MEK concentrations in air and water. These data indicate that MEK is generally below detection or, if detected, present at low concentrations in ambient air and drinking water (Appendix G4). MEK is not expected to partition and remain in soil based upon its physical-chemical properties.

**Ambient Air:**

Exposure from background ambient air and water are typically negligible. In its proposal to delist MEK from the CAA HAPs list, EPA concludes that ambient background air MEK exposures are not likely to have a significant influence on maximum annual exposures to MEK.<sup>66</sup> MEK is not detected in most ambient air samples which have been measured, with upper quartile measurement values being zero (Appendix G4 - National Ambient VOC Database - Shah and Heyerdahl 1988). In addition, EPA indicates that the AIRS database and California Air Toxics Database reports values ranging from Non-Detect (ND) to a high of 0.002 mg/m<sup>3</sup> (or 0.7 ppb, this occurs at the Houston ship channel and Providence, Rhode Island).

These air exposures are well below the RfC of 5 mg/m<sup>3</sup> (a factor of  $\geq 2500$  times lower). The RfC by definition is protective of the general population including potentially sensitive sub-populations (e.g. children). This RfC value includes total uncertainty factors of 300 to provide an additional margin of exposure beyond no effect levels of animal studies.

**Table 8.5 Ambient Air Exposures - Outdoor**

<b>Exposure Scenario</b>	<b>Air Concentration - Annual Average- (mg/m<sup>3</sup>)</b>
Typical	ND
Maximum	0.002 mg/m <sup>3</sup> annual max

Reviews (HSDB 2001; ATSDR 1992) report US ambient air concentrations that range from 0.01 - 14 ppb (0.00003-0.4 mg/m<sup>3</sup>). Data were often dated, not nationally representative, and from a variety of sources likely representing a range of averaging periods. The annual concentrations in AIRS or the daily concentrations in the National Ambient VOC database were considered best estimates of typical, chronic exposures. The highest reported ambient air levels were not point source specific and were for extreme urban environments such as Los Angeles, and are orders of magnitude lower than the RfC (14 ppb as compared to a RfC of 5 mg/m<sup>3</sup> [1.7 ppm]).

Potential for source specific air exposures are discussed under Section 8.6 and 8.7.

**Indoor Air:**

The highest reported indoor air concentrations (0.7 - 14 ppb or 0.002 - 0.04 mg/m<sup>3</sup>) are also well below the RfC (summary and detailed tables of air concentrations in Appendix G4). MEK was not detected in indoor air of schools (Appendix G4).

Data for schools were extremely limited. Four US school indoor air studies were identified. Only one specifically indicated that MEK was not detected (Sheldon *et al.* 1988), for three sampling locations in a Washington, DC elementary school. Three other studies of VOCs in

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<sup>66</sup> See 68 Fed. Reg. 32606 (May 30, 2003) (CAA delisting proposal).

indoor school air (Torres *et al.* 2002, Petronella *et al.* 2002, and AERIAS 2001) did not report detecting MEK, but references did not confirm if MEK was sampled (although another ketone, MIBK, was reported in the Torres study, and MEK was reported in other samples from AERIAS 2001). The Torres study examined a random sample of 120 classrooms in 30 schools in central and south Texas. The AERIAS study included over 3000 indoor air samples from schools, offices and homes. There is no reason to expect MEK in schools as no sources were identified unique to schools, potential combustion sources (*i.e.*, cooking, smoking) are lower in schools than residences, and greater room sizes and ventilation rates exist in schools than in residences (SRD cites 1.7 Air Changes per Hour as typical of schools from ASHRAE).

**Table 8.6 Residential Indoor Air Exposures**

Exposure Scenario	Air Concentration (mg/m <sup>3</sup> )
Bounding Estimate – Maximum Short-Term Concentration	0.04 mg/m <sup>3</sup> (14 ppb)

**Water:**

MEK is generally non-detectable in surface water and in drinking water and groundwater (WHO 1992; ATSDR 1992; USEPA National Drinking Water Contaminant Occurrence Database (NCOD) USEPA 2002a- Appendix G4). A single quantified value reported was confirmed to be in drinking water - this was a value of 1.6 ppb reported in a water sample from Iowa (Ogawa and Fritz 1985). The USEPA NCOD reported a value of 4.3 mg/L in one sample, whereas MEK was not detected in all other samples analyzed (67 total groundwater and surface water samples analyzed). USEPA indicates that the samples in the NCOD can be taken at any point in the water supply process within a treatment facility, including intake to final release as drinking water. It is not clear at what point this sample was taken. Given a concentration of 1.6 µg/L, and assuming ingestion of 1 L water/day (USEPA 1997a recommendation for 16-19 year olds, the greatest of all child age categories), would result in a total ingestion of 1 L X 1.6 µg/L = 1.6 µg MEK, indicating this potential exposure pathway is negligible. The Environmental Health Criteria document (WHO 1992) indicates that surface water concentrations are generally <100 µg/L and typically <1 µg/L. Based upon physical-chemical properties, MEK is expected to rapidly volatilize from open waters (as well as undergo degradation). In its proposal to remove MEK from the CAA HAPs list, EPA indicates that MEK's relatively rapid volatilization and rapid biodegradation in water indicate that humans are unlikely to be exposed to significant amounts of MEK in drinking water. Dermal exposure via bathing would also be minimal.

MEK has been detected in groundwater and leachate from hazardous waste sites and landfills (Appendix G4 - data from the 1980s). The source of MEK is not specified (bacterial generation or chemical disposal). Child contact with these media is not expected.

**Soil:**

Physical-chemical properties indicate that MEK partitioning to soil is minimal. A literature search did not identify any recent measurements of MEK in soil. Data from the 1980s listed in reviews (HSDB 2001; ATSDR 1992) only indicated MEK presence in soils directly at mines or waste disposal facilities. Child exposure would not occur in these settings.

## 8.5.2 General Population Biomonitoring Studies

Given that MEK is a natural human metabolite, naturally ubiquitous in foods, and also found in cigarette smoke, it is not unexpected that low levels would be detected in biomonitoring studies of the general population. The results reported in the studies below, in which participants did not have any known occupational exposures to MEK, all indicate low levels.

### Plasma:

NHANES Study: MEK was detected at low levels in adult blood during the NHANES surveys. The average blood concentration in 600 adults was 7.1 ppb MEK, with a 95th percentile of 16.8 ppb (Ashley *et al.* 1994). In a subsequent study analysis (NHANES), a positive dose-response effect was indicated for daily alcohol consumption and blood levels of MEK (Churchill *et al.* 2001). Presence in alcohol is consistent with MEK microbial production during fermentation processes. MEK occurs naturally in some alcoholic beverages, as well as many other food items (VCF 2000) and also may be added as a flavorant (Burdock 2002). In addition, ethanol inhibits the metabolism of MEK, leading to higher blood MEK concentrations (Liira *et al.* 1990). Sec-butanol, which is metabolized into MEK, also is found in some alcoholic beverages and many common food items.

### Breast milk:

Three studies were cited in the literature as reporting the presence of MEK in human breast milk: Urbach (1987), Pellizzari *et al.* (1982), and Erickson (1980). Urbach contains no information related to breast milk (rather, it describes analytical techniques for dairy milk). Pellizzari *et al.* (1982) and Erickson (1980) are the same study. The Erickson report contains more detailed information, including chromatograms. MEK was detected, not quantified in 5 of 8 breast milk samples analyzed. This study collected 42 samples of breast milk in women living in 4 urban areas: Bridgeville PA, Bayonne NJ, Jersey City NJ, and Baton Rouge LA. All 42 samples were analyzed. Eight of the 42 samples with the greatest number of analyte peaks or very intense unique peaks were selected for quantification and interpretation. For the eight samples for which the chromatograms were interpreted, MEK was detected in five of the eight samples. Background contamination was not fully characterized. Chromatogram peaks of MEK were relatively small compared to other analytes (Appendix G5).

Given that MEK is a natural human metabolite and of ubiquitous natural occurrence in food, the presence of low levels in serum or breast milk is not unexpected. It occurs naturally in mother's milk of other mammals (bovine, ewe, goat, buffalo) (VCF 2000; Singhal *et al.* 1997). The concentration of MEK in cow's milk increases with sample aging (Simon *et al.* 2001).

MEK would not be expected to bioconcentrate in breast milk, due to its rapid metabolism and excretion via breath and urine (Section 7.3). Also, its log  $K_{ow}$  of 0.29 does not indicate strong partitioning into lipids as opposed to aqueous substrates.

Assuming breast milk concentrations are at equilibrium with blood levels, based upon NHANES biomonitoring data, infant exposure via breast milk can be calculated as:

$$D_{\text{ext}} = \frac{C \times IR \times EF \times ED \times UCF}{BW \times AT \times 365 \text{ days/year}}$$

Where

$D_{ext}$  = External Dose (mg/kg/day)

C = Concentration (mg/kg)

IR = Ingestion Rate of breast milk (g/day)

EF = Exposure Frequency (365days/year)

ED = Exposure Duration (1 year)

AT = Averaging Time (1 year)

UCF = Unit Conversion Factor, here 1 kg/1000 g

BW = Body Weight (infant) (kg)

From the USEPA Child Specific Exposure Factors Handbook, average breast milk intake for ages birth to 12 months is 688 ml/day (709 g/day), with an upper percentile of 980 ml/day (1009 g/day). Conversion from ml/day to g/day is made using a density of 1.03 g/ml (USEPA 2002b).

Assuming a breast milk concentration equal to the 95<sup>th</sup> percentile blood concentration from NHANES (16.8 ppb) yields a potential exposure of 0.012 mg/day (mean intake) or 0.017 mg/day (maximum intake) for infants. Using a breast milk concentration equal to the average from NHANES (7.1 ppb) yields a potential exposure of 0.005 mg/day (mean milk intake) or 0.007 mg/day (maximum milk intake) for infants. On a weight basis (7.2 kg for 0-1 yr old) this equates to:

95<sup>th</sup> percentile estimated milk concentration, mean intake: 0.0017 mg/kg/day

95<sup>th</sup> percentile estimated milk concentration, maximum intake: 0.0024 mg/kg/day

Average estimated milk concentration, mean intake: 0.0007 mg/kg/day

Average estimated milk concentration, maximum intake: 0.001 mg/kg/day

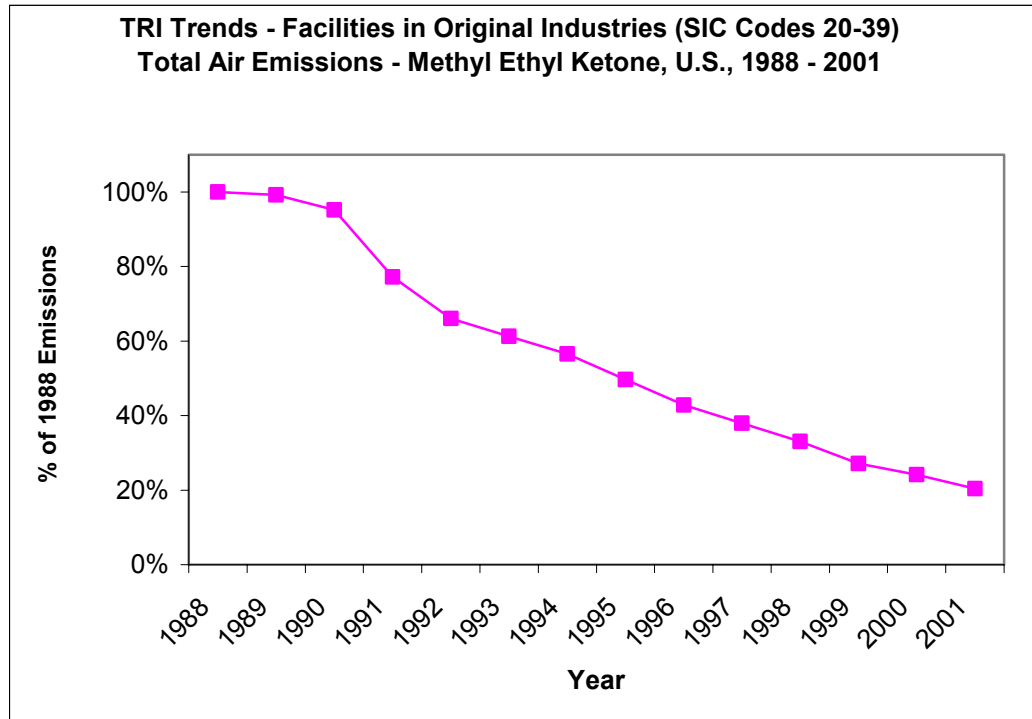
The estimates based upon mean intake are more appropriate for long-term averages (annual average daily dose). Potential infant exposure from breast milk for an occupationally exposed mother is discussed in Section 8.6.2.

## **8.6 Industrial Facility Related Exposures**

### **8.6.1 Facility Emissions**

Facilities have demonstrated reductions in MEK emissions over time. The trend report from the USEPA TRI Chemical Explorer indicates that overall air emissions have dropped to ~20% of 1988 emission for facilities in original industries (Figure 8.1).

Figure 8.6.1 Source of data : USEPA TRI Chemical Explorer 2003



As described earlier in this document (Section 3.3), EPA recently reviewed an in-depth analysis of potential for exposure from facility emissions, which included an extensive air dispersion modeling assessment as per EPA protocol.<sup>67</sup> The assessment addressed impacts of facility emissions by developing reasonable worst-case exposure scenarios based upon a single facility and also several sources located in close proximity. Details of this analysis, and EPA's assessment of it, are described in the Agency's proposal to remove MEK from the CAA HAP list. EPA's assessment:

- Confirmed that a conservative estimate of the highest maximum annual average concentration of MEK for all facilities modeled is approximately 1.2 mg/m<sup>3</sup>, at the entrance to an industrial park (non-residential area), and that the maximum annual average concentration for remaining emissions sources were all < 0.9 mg/m<sup>3</sup>.
- Judged that exposures to MEK of actual persons living in the immediate vicinity of an MEK emission source would more typically be at least a factor of 2-10 less than 1 mg/m<sup>3</sup>.
- Based upon the conservative nature of the modeling runs, the likely proximity of inhabitable areas and knowledge of human activity patterns, concluded that actual exposures will be far less than predicted exposures derived from this dispersion analysis.
- Concluded that these potential ambient exposures to MEK may not reasonably be anticipated to cause adverse human health effects.

<sup>67</sup> 63 Fed. Reg. 32606, 32621 (May 30, 2003) (proposal to remove MEK from CAA HAP list).

### 8.6.2 Occupational Exposures: Potential Child Exposure via Breast Milk Ingestion for an Occupationally Exposed Mother

Information presented in the hazard section demonstrates that MEK has a low potential for developmental and reproductive toxicity (Sections 7.6 and 7.7). Thus, occupational exposures of relevance for children would be those that could result in parental transfer to child. Transfer via adherence to parental skin or clothing is not a pathway for MEK, due to its volatility (any MEK on skin or clothing surface would evaporate before reaching home). Evaporation rate of a 0.01 cm thick film of MEK is 43 seconds based upon a vapor pressure of 91 mm Hg at 25°C) (Appendix G6). As per discussion in Section 8.5.3., MEK can partition into breast milk, but it is not expected to bioconcentrate due to its rapid metabolism and elimination from the body. The MEK octanol water partition coefficient does not predict significant bioconcentration in lipids. Ingestion of breast milk from an occupationally exposed mother was identified as the exposure pathway of most significance to children, and was further assessed. Fisher *et al.* (1997) estimated potential infant exposure to MEK via breast milk of an occupationally exposed mother. Due to the conservative nature of the assumptions in this study, the results are a bounding estimate of infant exposure (*i.e.*, an estimate that falls above the expected exposure range). It assumed the mother was exposed to a constant concentration at the TLV (200 ppm) throughout the workday. In addition, the infant was assumed to be nursed at intervals throughout the work period. Each nursing bout during the day was assumed to start 6 minutes after the occupational exposure stopped. To be conservative, the infant was further assumed to ingest a total of 920 ml during a 24 hour day, with 8 feedings of 115 ml each (whereas lactating women on average produce 680-840 ml breast milk /day and infants average 7-8 feedings per day).

This resulted in a predicted exposure estimate of 12.08 mg MEK/day for a nursing infant. The milk intake rate of 920 ml used in this study is closer to the upper percentile of breast milk ingestion (980 ml/day) rather than the mean ingestion rate (688 ml /day) as reported in the USEPA Child Specific Exposure Factors Handbooks (2002b). To scale this intake estimate to an annual average daily dose, an annual average daily intake of 688 ml/day was used, and a child body weight of 7.8 kg was used (average weight for a 2-12 month old, assuming that the mother returned to work full time when the child was 2 months old), and it was assumed that exposure was for 5 days/week, 40 weeks of the year (10 months):

Annual Average Daily Dose =

$$\frac{12.08 \text{ mg/day} \times (688/920 \text{ scaling factor}) \times 5 \text{ days/week} \times 40 \text{ weeks}}{7.8 \text{ kg} \times 365 \text{ days}}$$

This resulted in an annual average daily dose of 0.63 mg/kg/day

The conditions used in this estimate are not expected to occur. Many workplaces have a protective reassignment program for pregnant or nursing women, to minimize potential exposures. In addition, even without protective reassignment, continuous workplace exposure to the TLV is not expected to occur. Occupational MEK exposure levels reported for US workplaces (ATSDR 1992; HSDB 2001) were all well below the TLV; most values presented in these reviews were < 10 ppm (the highest 8 hr TWA occupational exposure level listed in the HSDB was 45 ppm for a study of male workers).

Further conservative assumptions that contribute to this being a bounding estimate (*i.e.*, an estimate that falls above the expected range of exposures) include:

- The infant was assumed to be fed intermittently throughout the workday, 6 minutes after the occupational exposure ended. Potential intake would decrease substantially for an infant that was not fed immediately after exposure, given rapid metabolism of MEK. A nursing mother in an occupational exposure setting is unlikely to have her infant at the job site. If milk were expressed and refrigerated or frozen to bring home, MEK would be expected to be lost during the warming process based upon its volatility.
- The assumption of more frequent infant feeding than typical, which increases the exposure estimate by allowing for less time for metabolic loss between feedings once maternal exposure has ended.

Methods to predict breast milk transfer are uncertain. However, for the reasons cited above, it is believed that the assumptions used in this assessment led to a bounding estimate of breast milk intake, and that the average potential for infant exposure via parental occupational exposure is much lower than this model prediction.

Adjusting this estimate downward by a factor of 4, based upon the highest reported occupational exposure level in the HSDB, results in an estimate of 0.16 mg/kg/day. It is believed that more current data for occupational exposures would show even lower exposure levels, and that workplace reassignment and adjustment for other factors listed above (*i.e.*, feeding frequency, longer time between exposure and feeding, and consideration of loss during heating of expressed milk) would further reduce the estimated potential for infant exposure via maternal milk.

## 8.7 Consumer Products

Table 8.4, Section 8.3.2.1 presents the broad categories of products that MEK may be found in. Literature and website reviews were performed to identify more specific uses of MEK, within each of the broad categories. A complete summary of all uses identified is found in Appendix G7. This initial review also includes possible products that might contain MEK, as listed on the Environmental Defense (ED) website based upon the broad categories contained in the EPA's Source Ranking Database (SRD) (Table G7.2).

In many cases, MEK is used in industrial applications where child exposure is not an issue. These applications were not considered further for children.

Product categories where child exposure could occur were identified and investigated further. Note, a number of these categories represented products that could "possibly" contain MEK. To narrow down this list, a comparison of information across 3 consumer product databases was performed (Table 8.7A-M): the EPA Source Ranking Database (basis of Environmental Defense listing); the EPA/MRI Household Product Database (Sack), the California Consumer Product Database (CARB) (Appendices G8-10). This comparison helped narrow down the specific products within a product category that might contain MEK.

Using the focused list, internet searches were performed for Material Safety Data Sheets (MSDSs) on products which might contain MEK to obtain more current data than available in the Sack and SRD reviews, which both contain pre-1990 product data (Appendix G11-summary of product MSDSs evaluated; note additional information on the Sack and SRD database are discussed in Appendix G15). Also, a home improvement store, a hobby shop, an auto supply store, and an Arts and Crafts store were visited to look at products that might contain MEK (Appendix G12). Photographs of purchased products are provided in Appendix G13.

These integrated data (Tables 8.7A-M) indicate MEK was not present in consumer products targeted specifically to children, with the exception of hobby model paints and glues targeted to older children and adults. In addition, for a given product type, MEK was not detected in many of the samples analyzed (Sack database, Appendix G9). Note, products are not identified by brand in Sack, but the Sack data are included in the SRD with brand identification in many cases. The SRD report only includes results for formulations that contained the chemical of interest; it does not report the number of formulations that did not contain this chemical.

Current MSDSs reported lower concentrations in product categories than the more dated information. When specific products by brand were matched up, in all cases current MSDSs reported lower concentrations than those in Sack, and in many cases MEK was no longer a product component. From the store visits, every product which contained MEK carried clear warning properties and directions to use under well ventilated conditions (see product photographs, Appendix G13). The integrated data were used to identify the consumer products with the greatest exposure potentials, for quantitative exposure estimation. The results of these product exposure assessments would also indicate if additional products should be considered.

### 8.7.1 Selection of Consumer Products for Exposure Estimation

By product category, this comparison found:

#### a) Automotive Cleaners (Table 8.7A)

SRD and Sack databases indicated that the following automotive cleaners could contain MEK:

Carburetor cleaner	<0.1 - 65%
Autobody polish and cleaner	12 - 61%
Tire cleaner/tire paint	<0.1 - 20%
Auto, transportation, and machinery paints including primer	2-34%
Gasket adhesives/removers	<0.1 - 31%
Transmission cleaner	<0.1 - 20%
Brake quieters/cleaners	<0.1 - 0.5%
Belt lubricants/dressings	<0.1 - 0.9%
Graffiti remover	0.96%
Solvents parts cleaners	0.22 - 0.33%

MEK was not detected in engine cleaner, automotive undercoat, battery cleaners/protectors, ignition wire dryers, tire puncture sealers, starting fluid spray, windshield de-icer, door spray lubricant, chrome protector/wash, vinyl top spray, upholstery cleaner, auto carpet cleaner, water pump lubricant, automotive sealant.

Carburetor cleaner had the highest weight fraction of all products for this category, with autobody polish and cleaner the second highest. In the Sack database, MEK was detected in 11 of 31 carburetor cleaners (range = 1.4-65% in items in which it was detected).

Autobody polish and cleaner is a category from SRD, N=3, 2 of which were identified (1 was business confidential). The 2 identified compounds were from Sack; they were both in the tire cleaner/tire paint category. For this category, MEK was <0.1% in 11 other products in Sack. The business confidential listing had the highest MEK content (61%) but could not be tracked further. The 2 other listings had MEK of 12 and 20%. Four MSDSs for autobody polish and cleaner were obtained from the internet, none reported MEK. Based upon a similar product

form (aerosol for 2 reported in Sack) and smaller product containers as compared to carburetor cleaner, modeling was performed with the carburetor cleaner scenario to represent a conservative estimate of exposure for an item in this category.

The category of auto, transportation, and machinery paints including primers was from SRD, and all entries were business confidential. It is not clear what these products represent, as the SRD category of aerosol paint concentrates includes results for auto body paints and primers. Thus, it appears that the auto, transport and machinery paint category likely represents industrial type applications. Indoor residential paint applications are more relevant for children's exposure, and are addressed in a separate section of this report.

MEK was reported in 1 of 11 gasket adhesive removers in the Sack database, a liquid product sold in a 2 fluid oz. container. Based upon lower product use/event, lower weight fraction, and liquid form, potential exposure via this product was considered low relative to an aerosol carburetor cleaner scenario. In addition, dermal and inhalation exposure from indoor use of liquid adhesives (at weight fractions greater than the liquid gasket adhesive remover) is addressed in a separate section.

The transmission cleaner weight fraction comes from one sample in Sack; it was below detection in eight other samples. The MSDS for this item was obtained, and MEK is not listed as an ingredient.

Thus, the use of a carburetor cleaner, based upon its greatest weight fraction was chosen to represent a worst-case analysis for this category. MSDSs for current products indicated, in all cases, lower MEK concentrations than values reported in Sack:

<u>Sack Value</u>	<u>Current Product MSDS</u>
65%	Not listed
20%	2-10%
20%	1-5%
18%	Not listed
12%	Not listed

**Table 8.7A Consumer Product Summary – Automotive Products**

Category or Product	Wt. Percentage in product (scale 0-100%) <sup>1</sup>			MSDS <sup>2</sup>	Store	Summary	
	CARB	SRD	SACK				
ED website indicates the following products may contain MEK: Auto, other transportation, and machinery refinish paints including primers; Automobile body polish and cleaners, other automotive chemicals							
SRD Category 289954300, includes carb/choke cleaner, brake cleaner, others unidentified	-	0.1 – 65	-	In addition to MSDSs below, not listed in 3 additional MSDSs for a glass cleaner, fuel injector cleaner, and a car spray cleaner		Exposure to these types of products could occur at home from teen use or passive exposure from parental use. Carburetor cleaner was selected for further evaluation, as its use is likely to result in the highest potential exposure based upon weight fraction range and aerosol form. Other products had lower MEK concentrations and were not adequately identified or were likely for industrial type applications (for example, transportation and machinery refinish paints). Also, spray paint use will be addressed under an indoor spray paint use scenario.	
Auto adhesive	2.08	-	-				
Carburetor and choke cleaner	1.41	-	<0.1 - 65	11 MSDSs, not listed in 8, others ranged from 1-10%; note Siloo brand is no longer made (was 65% in SRD), the company which makes Siloo products, CRC, markets a carb & choke cleaner that does not list MEK. All brands found in the SRD now had lower conc. or MEK wasn't listed	MEK found in 1 carb cleaner		
Brake quieters/ cleaners	0.22	-	<0.1 - 0.5	1 MSDS, not listed			
Gasket adhesives/ removers	-	-	<0.1 - 31				
Belt lubricants/dressings	-	-	<0.1 - 0.9				
Transmission cleaner	-	-	<0.1 - 18				
Tire cleaner/tire paint	NF		<0.1 - 20	2 MSDSs, not listed			
Autobody polish and cleaner	-	12 - 60.7	-	2 MSDSs, not listed			
Graffiti remover	0.96	-	-				
Auto, other transportation, and machinery refinish paints including primers	-	1.8 - 33.8	-	3 MSDSs, not listed in 1, found in 2 auto spray paints at 10% in each.	MEK found in auto spray paints		
Solvent parts cleaner, non-aerosol	0.33	-	-				
Solvent parts cleaner, aerosol	0.22	-	-				
SRD Category 289959700, includes gasket remover, wood plastic, correction fluid (0.002)	-	0.2 – 46	-				
<b>NOT FOUND IN THE FOLLOWING</b>							
Engine cleaner	-	-	<0.1	2 MSDSs, not listed	MEK not listed on engine cleaner		
Automotive undercoat	NF	-	<0.1				
Battery cleaners/protectors	-	-	<0.1				
Ignition wire dryers	-	-	<0.1				
Tire puncture sealers	NF	-	<0.1				
Starting fluid spray	-	-	<0.1				
Windshield de-icer	-	-	<0.1				
Door spray lubricant	-	-	<0.1				
Chrome protector/wax	NF	-	<0.1				
Vinyl top spray	NF	-	<0.1				
Upholstery cleaner	NF	-	<0.1				
Auto carpet cleaner	NF	-	-				
Water pump lubricant	-	-	<0.1				
Automotive sealant	NF	-	<0.1- <0.4				
Miscellaneous auto products	-	-	<0.1 - <0.4				
Note: NF = Not Found; "-" means no information in a database for a given product- for SRD it may be included in lumped information for the broader product category; <sup>1</sup> Databases are CARB = California Air Resources Board, SRD = Source Ranking Database, SACK = database provided from Thomas Sack for the work reported in Sack <i>et al.</i> 1992; <sup>2</sup> MSDS = Material Safety Data Sheet. Full database printouts and the MSDS summary are in Appendices G8-11. Details of the store visits are found in Appendix G12.							

**b) Household Cleaners/Polishes (Table 8.7B)**

Most products in this category did not contain MEK. MEK was found only in several fabric spot removers in low percentages (0.2-1.1%) in SRD and in a metal polish and cleanser (not indicated if this was an automotive or household product) at 1.86% in the CARB database. Current MSDSs for multiple products in this category did not list MEK as an ingredient. Based upon a low weight fraction and generally low amount of product per use, exposure potential via these products was considered to be minimal. Products with higher exposure potentials were chosen for evaluation.

**Table 8.7B Consumer Product Summary – Household Cleaners/Polishes**

Category or Product	Wt. Percentage in product (scale 0-100%) <sup>1</sup>			MSDS <sup>2</sup>	Store	Summary	
	CARB	SRD	SACK				
ED website indicates the following products may contain MEK: Household hard surface cleaners (aerosol), Household hard surface cleaners (liquid), Laundry starch preparations							
Household laundry starch-names indicate these are spot removers not starch	-	0.2-1.1	-	1 MSDS for a spot remover, not listed		Most products in this category did not contain MEK at detectable levels. Products in SRD were spot removers. Metal polish and cleanser would be used infrequently, and also had a low MEK content. MSDSs did not list MEK.	
Metal polishes and cleansers (not specified if auto or house)	1.86	-	-	4 MSDSs, not listed			
<b>NOT FOUND IN THE FOLLOWING</b>							
Toilet bowl cleaners	NF	-	-				
Hand dishwashing soap	NF	-	-	2 MSDSs for dishwasher detergent, not listed	Not Listed		
Heavy duty hand cleaner or soap	NF	-	-				
Stain remover	-	-	<0.1				
Furniture polish	NF	-	<0.1 - <0.6	2 MSDSs, not listed			
Floor wax	NF	-	<0.1 - <0.5				
Wax stripper	NF	-	<0.1				
Wood cleaner	-	-	<0.1				
Deodorizer/ disinfectant	NF	-	<0.1 - <0.3	2 MSDSs, not listed			
Oven cleaner	NF	-	<0.1 - <0.4	1 MSDS, not listed			
Laundry presoak	NF	-	<0.1				
Laundry starch	NF	-	-				
Laundry detergent	NF	-	-	3 MSDSs- for a bleach, softener, and detergent with bleach alternative, not listed			
Spray starch	-	-	-	1 MSDS, not listed			
Rug cleaner	NF	-	<0.1 - <0.2	1 MSDS, not listed			
Upholstery cleaner	NF	-	-				
Window cleaner		-	<0.1 - <0.3	2 MSDSs, not listed			
Bathroom cleaner	NF	-	<0.1 - <0.2				
Dip metal cleaner	-	-	<0.1				
General purpose spray cleaner	NF	-	<0.1	2 MSDSs, not listed			
Note: NF = Not Found. "-" means no information in a database for a given product- for SRD it may be included in lumped information for the broader product category. <sup>1</sup> Databases are: CARB = California Air Resources Board, SRD = Source Ranking Database, SACK = database provided from Thomas Sack for the work reported in Sack <i>et al.</i> 1992. <sup>2</sup> MSDS = Material Safety Data Sheet. Full database printouts and the MSDS summary are in Appendices G8-11. Details of the store visits are found in Appendix G12.							

**c) Paint-related Products (Table 8.7C)**

MEK was reported in all categories listed, including paint removers, paint thinners, spray paints and primers, aerosol wood stains and varnishes. The following products were chosen for exposure estimation: spray paint, aerosol woodstain/varnish, and paint thinner. The SRD database did not distinguish between spray paints and primers, and in Sack the highest weight fraction concentrations were reported for spray paints rather than primers. Thus, primers were not evaluated separately.

**Table 8.7C Consumer Product Summary – Paint Related Products**

Category or Product	Wt. Percentage in product (scale 0-100%) <sup>1</sup>			MSDS	Store	Summary
	CARB	SRD	SACK			
ED website indicates the following products may contain MEK: Aerosol paint concentrates, Architectural coatings, Miscellaneous paint related products, Other miscellaneous allied paint products, including brush cleaners, Paint and varnish removers, paint thinners, solvent thinned interior clear finishes, solvent thinned interior stains, solvent thinned interior undercoats and primers.						
Paint remover (also varnish removers in SRD)	0.04	0.2-72	<0.1 - 72	1 MSDS, 40-70%-specialized product - woodgrain and stripe remover		Estimated exposure for spray paint, aerosol wood stain/varnish and paint thinner use. In Sack, all primers which contained MEK were aerosols with the exception of one which was purple primer (this is a pipe cement), a 4 oz liquid container. Also, all Sack values for this category were below those in the spray paint category.
Paint thinner (SRD thinners for dopes, lacquers)	-	6-100	<0.1 - 72	Listed in 1 of 7 MSDSs. 25-30% in Jasco brush cleaner - Nasco brush cleaner was 65% in SRD	Pure MEK sold, also listed as an ingredient in a lacquer thinner and a roller and brush cleaner; not listed on all brands	
Spray paint	-	-	<0.1 - 54	24 MSDSs, not listed in 19, range 3.9 – 13%	Not listed on multiple brands of spray paints	
Aerosol paint concentrates, includes spray paints, primers, rust preventatives	-	3-65	-			
Solvent thinned interior undercoat	-	310 (sic)	-			
Wood stains, varnishes (solvent thinned interior clear coats and stains in SRD)	-	5.5-39	<0.1 - 55	22 MSDSs obtained, not listed in 20 including a brand in SRD which had 34-37% weight fraction, 2 aerosol Zipguard products had a 20% weight fraction, as compared to 39% in the SRD	Not listed on woodstain	
Primer/special primer	-	-	<0.1 - 310 (sic), 27.7 next highest	6 MSDSs, not listed		
Note: NF = Not Found. "-" means no information in a database for a given product- for SRD it may be included in lumped information for the broader product category. <sup>1</sup> Databases are CARB = California Air Resources Board, SRD = Source Ranking Database, SACK = database provided from Thomas Sack for the work reported in Sack <i>et al.</i> 1992. <sup>2</sup> MSDS = Material Safety Data Sheet. Full database printouts and the MSDS summary are in Appendices G8-11. Details of the store visits are found in Appendix G12.						

**d) Fabric and Leather Treatments (Table 8.7D)**

MEK was present in low concentrations in spray shoe polish and fabric spot remover in the Sack database. It was found at a high weight fraction (82%) in one 1-oz water repellent item. Current MSDSs for several products within these categories did not list MEK as an ingredient.

Given weight fractions and typical product use, exposures from these products were considered minimal compared to aerosol products already being evaluated (*i.e.*, spray paints, spray wood stains).

**Table 8.7D Consumer Product Summary – Fabric And Leather Treatments**

Category or Product	Wt. Percentage in product (scale 0-100%) <sup>1</sup>			MSDS	Store	Summary	
	CARB	SRD	SACK				
ED website indicates the following products may contain MEK: Shoe polishes and cleaners, waterproofing compounds							
Household laundry starch-names indicate these are spot removers not starch	-	0.2-1.1	-	1 MSDS for a spot remover - not listed		Most products in this category did not contain MEK at detectable levels. Products in SRD were spot removers. MSDSs did not list MEK. Of 41 water repellents analyzed in Sack, 39 were <0.1%, 1 was 0.2% and 1 was 82%. The 82% product was solid in a 1 oz size. In SRD, this is listed as Cadet Heel and Sole Water Repellent, a product that would be used infrequently. A lower value, of 0.2% was reported for Rain & Stain Shield	
Spray shoe polish	NF	0.1-8	<0.1-8	1 MSDS of shoe polish, not sure if spray, not listed			
Water repellent	-	0.2-82	<0.1-82	1 MSDS, not listed			
Vinyl & leather cleaners	NF	-	-				
Spot remover	NF	-	<0.1 - 1.1	1 MSDS, not listed			
Suede protector	-	-	<0.1				
Fabric protectants	NF	-	-	3 MSDSs not listed			
<b>NOT FOUND IN THE FOLLOWING</b>							
Fabric finisher	-	-	<0.1 - <0.3				
Anti-static spray	-	-	<0.1				
Note: NF = Not Found; ; "-" means no information in a database for a given product- for SRD it may be included in lumped information for the broader product category; <sup>1</sup> Databases are CARB = California Air Resources Board, SRD = Source Ranking Database, SACK = database provided from Thomas Sack for the work reported in Sack <i>et al.</i> 1992; <sup>2</sup> MSDS = Material Safety Data Sheet. Full database printouts and the MSDS summary are in Appendices G8-11. Details of the store visits are found in Appendix G12.							

**e) Cleaners for Electronic Equipment (Table 8.7E)**

In general, concentrations were low or below detection in these products, which are not intended for child use. The assessment focused on more relevant products.

**Table 8.7E Consumer Product Summary – Cleaners For Electronic Equipment**

Category or Product	Wt. Percentage in product (scale 0-100%) <sup>1</sup>			MSDS	Store	Summary	
	CARB	SRD	SACK				
SRD Category 284239700 cleaners such as tape head, video head cleaner, degreaser, contact cleaner, others non-identified	-	0.2-18	-			Low concentrations or below detection in products not intended for child use; assessment focused on more relevant products.	
Electronic cleaner	0.10	-	-				
Tape recorder cleaner	-	-	<0.1 - 0.9				
VCR cleaner	-	-	<0.1 - 0.3				
<b>NOT FOUND IN THE FOLLOWING</b>							
Electric shaver cleaner	-	-	<0.1				
Record cleaner	-	-	<0.1				
Record player cleaner	-	-	<0.1				
TV/Computer screen cleaner			<0.1				
Note: NF = Not Found; ; "-" means no information in a database for a given product- for SRD it may be included in lumped information for the broader product category; <sup>1</sup> Databases are CARB = California Air Resources Board, SRD = Source Ranking Database, SACK = database provided from Thomas Sack for the work reported in Sack <i>et al.</i> 1992; <sup>2</sup> MSDS = Material Safety Data Sheet. Full database printouts and the MSDS summary are in Appendices G8-11. Details of the store visits are found in Appendix G12.							

**f) Oils, Grease and Lubricants (Table 8.7F)**

Concentrations were low ( $\leq 1\%$ ) or below detection in these products, which are not intended for child use. The assessment focused on more relevant products.

**Table 8.7F Consumer Product Summary – Oil, Greases And Lubricants**

Category or Product	Wt. Percentage in product (scale 0-100%) <sup>1</sup>			MSDS	Store	Summary
	CARB	SRD	SACK			
ED website indicates the following products may contain MEK: Lubricating oils						
Silicone lubricant	-	-	<0.1 - 1			Low concentrations in products not intended for child use; assessment focused on more relevant products
Lubricant	0.11	0.2-8	<0.1 - 0.8			
Note: NF = Not Found; ; "-" means no information in a database for a given product- for SRD it may be included in lumped information for the broader product category; <sup>1</sup> Databases are CARB = California Air Resources Board, SRD = Source Ranking Database, SACK = database provided from Thomas Sack for the work reported in Sack <i>et al.</i> 1992; <sup>2</sup> MSDS = Material Safety Data Sheet. Full database printouts and the MSDS summary are in Appendices G8-11. Details of the store visits are found in Appendix G12.						

**g) Adhesive Related Products (Table 8.7G)**

MEK was identified in several types of adhesive products, including household synthetic resins and rubbers, and construction and panel adhesive. Current MSDSs did not identify MEK in any type of child-specific glue. A hobby store visit indicated it was contained in some hobby model glues. It was also identified in some construction and panel adhesives, but was not found in current MSDSs for carpet adhesive. For this category, products identified for evaluation were hobby model glue and general household use of adhesives. In addition, literature data for indoor air of new homes (and new cars) was used to represent potential for MEK exposure via construction/building type adhesive use.

**Table 8.7G Consumer Product Summary – Adhesive-Related Products**

Category or Product	Wt. Percentage in product (scale 0-100%) <sup>1</sup>			MSDS	Store	Summary
	CARB	SRD	SACK			
ED website indicates the following products may contain MEK: Synthetic resin and rubber adhesives						
Adhesive (synthetic resin and rubber in SRD)	-	0.2-100	<0.1 - 140 (sic)	These are all considered under the arts & crafts adhesive category		Adhesive use in home construction/repair will be addressed by a literature review of MEK in new homes (and new cars). Estimated inhalation and dermal exposures for hobby use and presence during adult use.
Wall paper remover/adhesive remover	-	-	<0.1			
Construction & panel adhesive	0.45	-	-	1 MSDS for weather strip adhesive - 20-30%		
Arts & crafts adhesive	2.84	-	-	32 MSDSs, not listed in 291, 50-70% in one clear household cement, 35-40% in one plastic cement for hobby models, 1-5% in one rubber cement	Not listed on multiple spray adhesives in an arts and crafts store. Listed in 1 specialty adhesive. One hobby glue and one hobby model kit indicated glue contained MEK.	
General purpose adhesive	2.77	-	-	Included under arts and crafts adhesive		
Contact adhesive	9.2	-	-			
Adhesive removers	1.85	-	<0.1	2 MSDSs, not listed		
Oil-resistant seal-all (glass, china, plumbing)	-	-	-		Listed	
Contact cement	-	-	-	Included under arts and crafts adhesive	Listed on several contact cements	
<b>NOT FOUND IN THE FOLLOWING</b>						
Aerosol adhesive (including industrial)	NF	-	-	Included under arts and crafts adhesive		
Carpet & tile adhesive	NF	-	-	5 MSDSs, not listed		
Woodworking glue	NF	-	-	Included under arts and crafts adhesive		
Note: NF = Not Found;; "-" means no information in a database for a given product- for SRD it may be included in lumped information for the broader product category; <sup>1</sup> Databases are CARB = California Air Resources Board, SRD = Source Ranking Database, SACK = database provided from Thomas Sack for the work reported in Sack <i>et al.</i> 1992; <sup>2</sup> MSDS = Material Safety Data Sheet. Full database printouts and the MSDS summary are in Appendices G8-11. Details of the store visits are found in Appendix G12.						

**h) Miscellaneous Products (Table 8.7H)**

Weight fractions were generally low. Higher weight fractions were reported for industrial type products (*i.e.*, gravure inks) or vague products (miscellaneous non-automotive). Products from other categories were considered to be more relevant for child exposure.

**Table 8.7H Consumer Product Summary – Miscellaneous Products**

Category or Product	Wt. Percentage in product (scale 0-100%) <sup>1</sup>			MSDS	Store	Summary	
	CARB	SRD	SACK				
ED website indicates the following products may contain MEK: Nonstructural caulking compounds and sealants, Acid non-household metal cleaners (liquid), Gravure inks; Other industrial chemical specialty products; Misc. use aromatics; Other specialty cleaning and sanitation products; Specialty performance sealants; Surfactants, finishing agents, and assistants							
Specialized cleaner	-	-	<0.1 - 0.2			Other consumer product scenarios were more relevant for children. Correction fluid has a low weight percent of MEK (<0.10.2 %), is sold in small containers (Typical container is ≤1oz.), and used in small quantities.	
Acid non-household metal cleaner	-	3	-				
All purpose liquid cleaner	-	-	<0.1-0.2				
Miscellaneous non-automotive	-	-	<0.1 - 48				
Correction fluid	-	0.2	<0.1 - 0.2				
Multipurpose solvents	2.36	-	-				
Gravure inks (nonspecific)	-	40	-				
<b>NOT FOUND IN THE FOLLOWING PRODUCTS</b>							
Rust remover	-	-	<0.1				
Caulking	NF	-	<0.1 - <0.4		Not listed		
Note: NF = Not Found; ; "-" means no information in a database for a given product- for SRD it may be included in lumped information for the broader product category; <sup>1</sup> Databases are CARB = California Air Resources Board, SRD = Source Ranking Database, SACK = database provided from Thomas Sack for the work reported in Sack <i>et al.</i> 1992; <sup>2</sup> MSDS = Material Safety Data Sheet. Full database printouts and the MSDS summary are in Appendices G8-11. Details of the store visits are found in Appendix G12.							

**i) Agricultural / Pesticide Products (Table 8.7I)**

This category was not in Sack or SRD. The CARB database did not report MEK in any of these materials, and MEK was not listed in 1 product MSDS. This category was not evaluated further. Note subsequent literature review indicated that MEK might be contained as an inert material in pesticides applied to crops. Given MEK's rapid volatilization (43 sec for a 0.01 cm surface film, Appendix G6), biodegradation and photodegradation, pesticide inert use would not be expected to be a significant pathway of child exposure, with negligible amounts expected to be present in food items.

**Table 8.7I Consumer Product Summary – Agricultural/Pesticide Products**

Category or Product	Wt. Percentage in product (scale 0-100%) <sup>1</sup>			MSDS	Store	Summary	
	CARB	SRD	SACK				
ED website indicates the following products may contain MEK: Miscellaneous agricultural/pesticidal products							
Not in SRD or Sack	-	-	-	1 MSDS for a pesticide product, not listed		CARB database indicates not in pesticides, this category not evaluated further.	
<b>NOT FOUND IN THE FOLLOWING PRODUCTS</b>							
Herbicides and defoliant	NF	-	-				
Flea and tick insecticide	NF	-	-				
Wasp & hornet insecticide	NF	-	-				
Lawn & garden insecticide	NF	-	-				
Crawling bug insecticide	NF	-	-				
Insecticide foggers	NF	-	-				
Insect repellants	NF	-	-				
Fungicides & nematocides	NF	-	-				
Note: NF = Not Found; ; "-" means no information in a database for a given product- for SRD it may be included in lumped information for the broader product category; <sup>1</sup> Databases are CARB = California Air Resources Board, SRD = Source Ranking Database, SACK = database provided from Thomas Sack for the work reported in Sack <i>et al.</i> 1992; <sup>2</sup> MSDS = Material Safety Data Sheet. Full database printouts and the MSDS summary are in Appendices G8-11. Details of the store visits are found in Appendix G12.							

**j) Personal Hygiene Items (Table 8.7J)**

This category is not in SRD or Sack. MEK was not reported in any material in this category in the CARB database. In addition, it was not reported in MSDSs for hair products. Further searching was done to try to identify if MEK was used in cosmetics (other than nail polish and nail polish remover, which are addressed in the next category). MEK was not reported in an analyses of volatiles from 31 consumer products that included cologne, perfume, hairspray, air freshener, fabric softener, deodorant/anti-perspirant, moisturizer and a nail enamel remover (Table 6.2 in Cooper *et al.* 1992). Common Fragrance and Flavor Materials (Bauer *et. al.* 1990) indicates that aliphatic monoketones are of minor importance as fragrance and aroma substances, with the exception of some higher MW odd-number ketones C7 and greater. Introduction to Perfumery (Curtis and Williams 1994) also indicates that few aliphatic straight-chain and branched-chain ketones are used as aroma chemicals. The 2001 Database of Perfumery Materials and Performance indicates that MEK may be used as a solvent in compounds for cosmetic and technical purposes, e.g. lipsticks (PMP 2001). This is likely use as an extraction solvent. An email from John Leffingwell indicates (1/20/03) that MEK is primarily used as an extraction solvent or in chemical synthesis in the Flavor & Fragrance industry and only occasionally used as an intended added ingredient for flavors or perfumes. Based upon this information, products in this category were not evaluated further.

**Table 8.7J Consumer Product Summary – Personal Hygiene Items**

Category or Product	Wt. Percentage in product (scale 0-100%) <sup>1</sup>			MSDS	Store	Summary	
	CARB	SRD	SACK				
EPA Fact Sheet indicates MEK is used in cosmetic production; HSDB indicates use as a fragrance in perfumes is discontinued; EHC indicates MEK is an intermediate used in the manufacturing of perfumes							
Not in SRD or Sack						Not found in CARB database or search of fragrance and cosmetics websites <sup>68</sup> .	
<b>NOT FOUND IN THE FOLLOWING PRODUCTS</b>							
Underarm anti perspirants and deodorants	NF	-	-				
Astringents/toners	NF	-	-				
Body lotions	NF	-	-				
Personal fragrance products	NF	-	-				
Hair spray	NF	-	-	4 MSDSs for hair products - not listed. 2 MSDSs were for hair sprays, 2 for hair colors			
Hair mousse	NF	-	-				
Hair shines	NF	-	-				
Hair gel	NF	-	-				
Rubbing alcohol	NF	-	-				
Shaving cream or gel	NF	-	-				
Foot powder	NF	-	-				
Personal hygiene spray	NF	-	-				
Note: NF = Not Found; ; "-" means no information in a database for a given product- for SRD it may be included in lumped information for the broader product category; <sup>1</sup> Databases are CARB = California Air Resources Board, SRD = Source Ranking Database, SACK = database provided from Thomas Sack for the work reported in Sack <i>et al.</i> 1992; <sup>2</sup> MSDS = Material Safety Data Sheet. Full database printouts and the MSDS summary are in Appendices G8-11. Details of the store visits are found in Appendix G12.							

<sup>68</sup> The following websites were searched for information on methyl ethyl ketone and butanone use: www.fpinva.org (website for Fragranced Products Information Network), www.cir-safety.org (website for Cosmetic Ingredient Review), http://www.iff.com/ingredients.nsf/home (website for International Flavor and Fragrances). For all, no use information specific to MEK or butanone was found.

**k) Nail Care Products (Table 8.7K)**

MEK was reported in very low concentrations (0.2% in nail polish and 0.05% in nail polish remover) in these products. Given low concentrations and typical low mass of product/use, these products were not evaluated further.

**Table 8.7K Consumer Product Summary – Nail Care Products**

ED website indicates the following products may contain MEK: Nail enamel and polish removers, other manicure preparations						
Category or Product ID	Wt. Percentage in product (scale 0-100%) <sup>1</sup>			MSDS	Store	Summary
	CARB	SRD	SACK			
Nail polish	0.2	-	-	2 MSDSs, not listed		Found in nail polish and remover at lower weight fractions <1%. Typical nail polish containers are 15 ml.
Nail polish remover	0.05	-	-			
Nail base coats, undercoats	NF	-	-			
Note: NF = Not Found; ; "-" means no information in a database for a given product- for SRD it may be included in lumped information for the broader product category; <sup>1</sup> Databases are CARB = California Air Resources Board, SRD = Source Ranking Database, SACK = database provided from Thomas Sack for the work reported in Sack et al. 1992; <sup>2</sup> MSDS = Material Safety Data Sheet. Full database printouts and the MSDS summary are in Appendices G8-11. Details of the store visits are found in Appendix G12.						

**l) Household Miscellaneous (Table 8.7L)**

In SRD, MEK was reported in writing and stamp pad inks, markers, and other art materials (not specified). Multiple MSDSs were obtained for products in these categories, especially for products marketed for children’s use, but including permanent markers and dry erase materials. MEK was not listed on any of these MSDS for inks, markers, and most children’s products were labeled to be in conformance with ASTM D4236. MEK was found in hobby model paint. This category will be addressed with a hobby model paint scenario.

**Table 8.7L Consumer Product Summary – Household Miscellaneous**

ED website indicates the following products may contain MEK: Household tints and dyes; Inks, writing and stamp pad inks (excl drawing and printing inks), Markers, fine point and broad tipped, Other art materials including clay, water and tempera colors, finger paint, etc.,						
Category or Product ID	Wt. Percentage in product (scale 0-100%) <sup>1</sup>			MSDS	Store	Summary
	CARB	SRD	SACK			
Writing and stamp pad inks	-	8.3	-	3 MSDSs, not listed		Multiple MSDSs did not indicate MEK, except for hobby paint.
Markers, fine point and broad	-	19.6	-	8 MSDSs for a variety of markers, (children's markers, Sharpies®), did not report MEK and many children's markers conformed to ASTM D4236		
Other art materials including clay, water and tempera colors, finger-paints, etc.	-	6.2 - 30	-	13 MSDSs for paints, not listed in 12, 15-20% in one AeroGloss® paint for hobby model use. Not listed in 6 MSDSs for modeling clays. Not listed in 1 MSDS for crayons.	Numerous paints adhesives, and model kits did not list MEK. MEK was found in one brand of paints and indicated to be in the glue of one car model kit (the latter was considered under the adhesive category).	
Household tint & dye	-	7.5	-			
Pens	-	-	-	4 MSDSs, not listed		
Pen and whiteboard cleaners	-	-	-	4 MSDSs, not listed		
Note: NF = Not Found; ; "-" means no information in a database for a given product- for SRD it may be included in lumped information for the broader product category; <sup>1</sup> Databases are CARB = California Air Resources Board, SRD = Source Ranking Database, SACK = database provided from Thomas Sack for the work reported in Sack <i>et al.</i> 1992; <sup>2</sup> MSDS = Material Safety Data Sheet. Full database printouts and the MSDS summary are in Appendices G8-11. Details of the store visits are found in Appendix G12.						

**m) Other Construction Related Items (Table 8.7M)**

MEK was reported in some construction-related materials. Air concentrations for a new home and a new car were considered to better evaluate potential exposure via construction related items. Exposure via use of pipe cement and primer was also evaluated.

**Table 8.7M Consumer Product Summary – Other Construction Product Related Categories**

ED website indicates the following products may contain MEK: Industrial particleboard (furniture, fixtures, cabinets, etc.), General performance sealants (PVAC, butyl, vinyl, etc.)						
Category or Product ID	Wt. Percentage in product (scale 0-100%) <sup>1</sup>			MSDS	Store	Summary
	CARB	SRD	SACK			
Particleboard	-					Scenario of a new home used to represent a worst case scenario for exposure to MEK via use in home construction products. Pipe cement and primer: considered literature and use information to better understand potential exposure.
General performance sealant	-	12.1	-			
Other miscellaneous including putty, gla... (title unfinished in database printout)	-	20-29.8	-		Not listed on putties	
Wood fillers	26	-	-		Not listed	
Pipe Cement & Primer	44.59	-	-	MSDSs for pipe cement, not listed in 2, was 35-45% in one and 17% in one	Listed	
Pipe Joint Cleaners	-	-	-		Not listed	

Note: NF = Not Found; ; "-" means no information in a database for a given product- for SRD it may be included in lumped information for the broader product category; <sup>1</sup>Databases are CARB = California Air Resources Board, SRD = Source Ranking Database, SACK = database provided from Thomas Sack for the work reported in Sack *et al.* 1992; <sup>2</sup>MSDS = Material Safety Data Sheet. Full database printouts and the MSDS summary are in Appendices G8-11. Details of the store visits are found in Appendix G12.

**8.7.2 Summary of Products to be Evaluated and Exposure Scenarios**

Based upon this integrated information, the following products and scenarios were identified as potential pathways for child exposure to MEK associated with consumer product use:

- 1) Carburetor cleaner (aerosol): teenage use in garage, infant passive presence in house
- 2) Spray Paint: teenage use indoors, infant passive presence elsewhere in house
- 3) Wood stain/ varnish (aerosol): teenage use indoors, infant passive presence elsewhere in house
- 4) Paint thinner (liquid):
  - a) use as an addition to wood varnish: teenage use indoors, infant passive presence elsewhere in house
  - b) use as a brush cleaner- inhalation exposure, an open can containing paint brushes: teenage use indoors, infant passive presence elsewhere in house.,
  - c) use in clean-up - teenage dermal exposure
- 5) Adhesives (household, liquid)-
  - a) hobby use, inhalation: teenage use indoors and infant passive presence; i) in same room during use and also; ii) elsewhere in house
  - b) hobby use, dermal: teenage use
  - c) adult use in a home application: teenage and infant passive presence; i) in the same room during use and also; ii) elsewhere in house
- 6) Hobby model paints (liquid): teenage use indoors and infant passive presence; i) in the same room during use and also; ii) elsewhere in house.
- 7) Construction materials and adhesives
  - a) new car and new home: review of measured air data

- b) pipe cement and primer: potential for exposure addressed through literature data and also use information.

Exposures that will be minimal based upon concentration in product and typical amount of product used (products sold in small volume containers as well, limiting worst-case exposure scenarios- typical volume information from Sack database when available):

Laundry spot remover (1.1% weight fraction, 8 oz.)  
Metal polish and cleanser (1.9% weight fraction)  
Spray shoe polish (0.1 - 8% weight fraction, 5 oz.)  
Water repellent for material (<0.1 - 0.2% weight fraction)  
Heel and Sole Water Repellent - 82% MEK, sold in 1 oz size. Children unlikely to use this product frequently  
Cleaners for electronic equipment (<0.1 - 18% MEK, 2 oz)  
Lubricants (<0.1 - 0.8% MEK, 0.05 - 6 oz)  
Correction fluid (0.2% MEK, 1 oz)  
Nail polish (0.2% MEK, typical volume = 15 ml = 0.5 oz)

Note, use of a consumer product represents an acute, rather than chronic, exposure scenario. Exposures are short-lived and periodic, rather than continuous over time. Due to MEK's rapid metabolism and elimination from the body, carry-over of body burden between events is unlikely unless time between occurrence is very brief.

The purpose of this assessment was to develop child exposure estimates from use of MEK containing products, and so all exposure modeling assumed MEK present in the product. The likelihood of MEK presence was not considered in the modeling studies (*i.e.*, non-detects were not included in the weight fraction distributions). Also, because weight fraction data were not available for the full range of consumer products, but only a subsample, a quantitative adjustment for frequency of use of an MEK containing product was not made when adjusting single day estimates to a chronic basis based upon frequency of use. Thus, the chronic estimates provided are expected to be bounding estimates, and fall above the range of child exposures likely from MEK use.

Detailed descriptions of modeling approach and assumptions, models and input data, and results are presented in Appendix G14. Only summary results are provided below. Potential dose rates provided in the summary tables are adjusted for an inhalation uptake fraction of 0.5 for MEK (ATSDR 1992; WHO 1992; Morgott *et. al.* 2001 - more detailed discussion of inhalation uptake fraction is presented in Appendix G14). For all scenarios, chronic estimates were calculated using the 90<sup>th</sup> percentile for frequency of use and the median exposure estimate, consistent with the approach in EPA's E-FAST model. The chronic estimates also assume a maximum use frequency for every year (whereas E-FAST defaults typically assume a number of years without exposure). In addition, chronic estimates assume every product use occurs indoors, whereas for many of the products evaluated outdoor use is more frequent (Westat 1987 - details of split between indoor/outdoor use are found in Appendix G14).

### **8.7.3 Consumer Product Exposure Assessment Results**

#### **1) Product 1. Carburetor Cleaner**

Exposure was modeled using the aerosol spray module of E-FAST. Results below are for acute (day of use) exposures for teen users and also all passive presence of all ages. Details of modeling are in Appendix G14. Indoor use of carburetor cleaner is an infrequent occurrence for only a fraction of the population that used this product (Westat 1987). The scenario modeled was use in a residential garage (68 m<sup>3</sup>), with the door open but no active ventilation. It was considered that older children might also be exposed to automotive products during a shop

class in a vocational-technical high school. The residential indoor garage scenario, however was modeled to represent a worst case. The school setting would have a much larger room volume and also much greater ventilation rate, resulting in lower exposures than a residential use. Further, use of carburetor cleaner, which was chosen to represent a worst-case automotive use, would be expected to be low in a school shop setting given that maintenance of today's vehicles no longer requires this product.

**Table 8.8 Carburetor Cleaner - Exposure Modeling Results**

Exposure Scenario		4 hr TWA (mg/m <sup>3</sup> )	Acute Dose Rate (ADR) by age in mg/kg/day					Comments	
			<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs		16-19 yrs
Maximum Use: Day of Use	Passive	1.24	0.07	0.06	0.05	0.04	0.03	0.02	Upper use- 271 g, maximum MSDS weight fraction, 68m <sup>3</sup> garage size and 10.6 Air Changes per Hour (ACH)
	Active	3.87	-	-	-	-	-	0.07	
Median Use: Day of Use	Passive	0.33	0.017	0.015	0.013	0.011	0.007	0.006	Median use -143 g, median MSDS weight fraction
	Active	1.01	-	-	-	-	-	0.018	
			Annual Average Daily Dose (Chronic Dose Rate) by age in mg/kg/day						
Median Use: Chronic Estimate	Passive	-	0.0003	0.0003	0.0002	0.0002	0.0001	0.0001	Chronic estimated using median use exposure and 90th percentile frequency of occurrence per year (6), every year
	Active	-	-	-	-	-	-	0.0003	

## 2) Product 2. Spray Paint

Exposure was modeled using the aerosol spray module of E-FAST. Results below are for acute (day of use) exposures for teen users and also all passive presence of all ages. Details of modeling are in Appendix G14. Indoor use is an infrequent occurrence for only a fraction of the population (Westat 1987). Frequency for chronic estimate was based upon adult use and frequency of all uses (indoor and outdoor) and is greater than likely indoor use. MEK was not found in typical spray paints in store visits (rather, it appears to be more in specialty enamels, auto sprays- products that are even more likely to be used outdoors than household spray paints).

**Table 8.9 Spray Paint - Exposure Modeling Results**

Exposure Scenario		4 hr TWA (mg/m <sup>3</sup> )	Acute Dose Rate (ADR) by age in mg/kg /day						Comments
			<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs	16-19 yrs	
Maximum Use: Day of Use	Passive	19.87	1.04	0.93	0.81	0.64	0.41	0.35	Upper use- 1 can, 40 m <sup>3</sup> room, 1.34 ACH, maximum MSDS weight fraction
	Active	56.00	-	-	-	-	-	0.99	
Median Use: Day of Use	Passive	9.38	0.49	0.44	0.38	0.30	0.19	0.17	Median use amount, median MSDS weight fraction
	Active	26.58	-	-	-	-	-	0.47	
			Annual Average Daily Dose (Chronic Dose Rate) by age in mg/kg/day						
Median Use: Chronic Estimate	Passive	-	0.008	0.007	0.006	0.005	0.003	0.003	Chronic estimate using median use exposure and 90th percentile frequency of uses/yr (6)
	Active	-	-	-	-	-	-	0.008	

**3) Product 3. Wood Stain/Varnish (aerosol)**

Exposure was modeled using the aerosol spray module of E-FAST. Results below are for acute (day of use) exposures for teen users and also for passive presence of all ages. Details of modeling are in Appendix G14. Indoor use is likely an infrequent occurrence for only the fraction of population that uses this product. Frequency of use for chronic estimate is based upon adults who used this product. A refined modeling scenario was performed with PROMISE for a teen user for the maximum use scenario, which allowed for a consideration of room size distributions during use (based upon use information from Westat 1987- Appendix G14).

**Table 8.10 Wood Stain/Varnish (Aerosol) – Exposure Modeling Results**

Exposure Scenario		4 hr TWA (mg/m <sup>3</sup> )	Acute Dose Rate (ADR) by age in mg/kg/day						Comments
			<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs	16-19 yrs	
Maximum Use: Day of Use	Passive	30.34	1.59	1.42	1.23	0.98	0.62	0.54	Upper use-1 can- 371 g, 40 m <sup>3</sup> room, 1.34 ACH, maximum MSDS weight fraction ( only listed on 1 MSDS)
	Active	91.88	-	-	-	-	-	1.62	
This consumer product scenario led to the highest potential exposures and was refined using the PROMISE model and an estimate of room size distributions for use indoors. The maximum use amount and maximum MSDS weight fraction were still used:									
PROMISE MODEL Maximum Use: Day of Use; Room Size Distribution	Active	4 hr TWA: mean= 65 mg/m <sup>3</sup> , 10th-90th percentiles = 26-85 mg/m <sup>3</sup> For a 16-19 year old ADR (in mg/kg/day): mean = 1.1, median = 1.2, 10th-90th percentiles = 0.46 - 1.55						PROMISE was run, using conditions which gave the same maximum exposure as E-FAST	
Median Use: Day of Use	Passive	18.67	0.98	0.87	0.76	0.60	0.38	0.33	Median use -228 g for combined indoor and outdoor use, 0.2 weight fraction, 1.34 ACH
	Active	56.52	-	-	-	-	-	1.00	
			Annual Average Daily Dose (Chronic Dose Rate) by age in mg/kg/day						
Median Use: Chronic Estimate	Passive	-	0.016	0.014	0.012	0.010	0.006	0.005	Chronic estimated using median use exposure and 90th percentile frequency (6/yr)
	Active	-	-	-	-	-	-	0.016	

#### 4) Product 4: Paint Thinner (liquid)

MEK in particular is a specialty application thinner. The largest size it was sold in at a home improvement store was 32 oz, at a cost greater than other thinners (Appendix G13- store visit) (although an MSDS for both a quart and a gallon size container was found on the internet). It is used for thinning and cleanup of solution vinyl coatings, epoxy coatings, urethane coatings, and other high performance, chemical resistant coatings. It may be contained in other thinners.

The MEK can was clearly marked with warning labels (Appendix G13 product photographs): “Whenever possible, use outdoors in an open air area. Do not use in areas where vapors can accumulate and concentrate such as basements, bathrooms or small enclosed areas. USE ONLY WITH ADEQUATE VENTILATION TO PREVENT BUILDUP OF VAPORS. Open all windows and doors. Use only with a cross-ventilation of moving fresh air across the work area. If strong odor is noticed or you experience slight dizziness, headache, nausea or eye-watering- STOP - ventilation is inadequate. Leave area immediately.”, and also indicates: “It is intended for occasional use only.”

MEK is both sold as a pure product for lacquer thinning, and can also be identified as a constituent in other paint thinners. An informal poll of home do-it-yourselfers indicates that paint thinners mostly would be used for clean up. They would be added to some thicker paints at a low rate (1-2 oz/gallon).

### **Scenario A) Addition to Coating**

This product would be expected to be added in minimal quantity to the types of materials listed above. Of those materials, the coating product that might be used residentially in the greatest amount would be a urethane floor or wood finish- these products have high odor and ventilation is desired as well to help in speeding product drying time.

The item category considered most similar in Westat (1987) was wood stain/varnishes/finishes. For the wood stain/varnish/finish category, 10th percentile use = 4 oz, 50th percentile = 16 oz, 90th = 128 oz. Modeling assumes that 100% MEK was added to wood stain at 1 oz/gallon (0.008 weight fraction) or 2 oz/gallon (0.016 weight fraction).

Exposure was modeled using the latex paint module of E-FAST. Results below are for acute (day of use) exposures for teen users and also all passive presence of all ages. Details of modeling are in Appendix G14. Note, frequency of paint thinner use (12/year- Westat 1987) seems high for general population. This scenario assumes 100% MEK was added to woodstain/varnish. This use is likely an infrequent occurrence for a fraction of the population.

**Table 8.11 Paint Thinner - Exposure Modeling Results**

Exposure Scenario		4 hr TWA (mg/m <sup>3</sup> )	Acute Dose Rate (ADR) by age in mg/kg/day						Comments
			<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs	16-19 yrs	
Maximum Use: Day of Use	Passive	0.54	0.03	0.03	0.02	0.02	0.01	0.01	Upper use - 3584 g, 40 m <sup>3</sup> , 1.34 ACH, paint at 0.016 weight fraction MEK (2 oz/gallon)
	Active	1.91	-	-	-	-	-	0.03	
Median Use: Day of Use	Passive	0.03	0.002	0.002	0.001	0.001	0.001	0.001	Median paint use, 40 m <sup>3</sup> , 1.34 ACH, 0.008 weight fraction (1 oz MEK/gallon)
	Active	0.12	-	-	-	-	-	0.002	
			<b>Annual Average Daily Dose (Chronic Dose Rate) by age in mg/kg/day</b>						
Median Use: Chronic Estimate	Passive	-	5.9E-05	5.3E-05	4.5E-05	3.6E-05	2.3E-05	2.0E-05	Chronic estimated using median use exposure and 90th percentile frequency of occurrence (12) per year, every year
	Active	-	-	-	-	-	-	7.0E-05	

**Scenario B) Use in Clean-up: Evaporation from Open Container**

This scenario was modeled using PROMISE (Appendix G14).

**Table 8.12 Assumptions for PROMISE modeling for evaporation during brush cleaning**

<b>Container size</b>	5 inch diameter. Radius = 2.5 inches = 6.35cm; Area = (3.14) X (6.35) <sup>2</sup> = 127 cm <sup>2</sup>	Could fit a brush in but not have the brush fall over (~1 inch wider than a typical coffee can) (professional judgment)
<b>Duration</b>	10 min	Estimate of time spent brush cleaning (professional judgment)
<b>Weight fraction</b>	1	Assume 100% MEK
<b>Room size</b>	Active use - 20 m <sup>3</sup> Passive use - 369 m <sup>3</sup> (House size)	For active use, estimated that this could be done in a small room. For passive use, since PROMISE is a single zone model, a typical house volume was used (professional judgement).
<b>ACH</b>	1.34	Open ventilation

**Table 8.13 Evaporation of pure MEK from open can during brush cleaning - Exposure Modeling Results**

Exposure Scenario		4 hr TWA (mg/m <sup>3</sup> )	Acute Dose Rate (ADR) by age in mg/kg/day						Comments
			<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs	16-19 yrs	
Maximum Use: Day of Use	Passive	0.7	0.038	0.035	0.030	0.024	0.015	0.013	PROMISE model, pure MEK, evaporation from open can, 369 m <sup>3</sup> room (simulate one house-size room), 10 min scenario
	Active	13.7	-	-	-	-	-	0.24	PROMISE model, evaporation from open can, 20 m <sup>3</sup> room, 10 min scenario
			Annual Average Daily Dose (Chronic Dose Rate) by age in mg/kg/day						
Maximum Use: Chronic Estimate	Passive	-	0.0013	0.0011	0.0010	0.0008	0.0005	0.0004	Chronic estimated using 90th frequency (12) every year
	Active	-	-	-	-	-	-	0.008	

**Scenario C) Use in Clean-up: Dermal Exposure - Teen Age Use Only**

The scenario was a teen using a rag to rub paint thinner on their skin. The scenario assumed a 10 second contact time with each area of skin, and that 3/4 of each hand was contacted. This scenario would also have an inhalation component, but given the amount of material used and exposure duration, inhalation from this scenario would be expected to be lower than from the higher use inhalation scenarios already assessed.

Spreadsheet analysis for absorbed dose =

$$D_{INT} = \frac{C \times K_p \times SA \times ED \times UCF}{BW \times AT}$$

- Where  $D_{INT}$  = Internal Dose
- C = Concentration
- $K_p$  = Skin Permeability Coefficient
- SA = Surface Area (exposed skin)
- ED = Exposure Duration
- BW = Body Weight
- AT = Averaging Time
- UCF = Unit Conversion Factor

A measured aqueous skin permeability coefficient for MEK is 0.005 cm/hr (USEPA 1992), determined *in vitro* from human skin. USEPA dermal exposure assessment guidance indicates that full-term infants have completely functional stratum corneum, with excellent barrier properties, thus the measured  $K_p$  value is applicable to children and teens (USEPA 1992).

For pure MEK, the skin permeability coefficient can be calculated from the aqueous skin permeability coefficient as (USEPA 1992):

$$K_{p_{neat}} = K_{p_{water}} \times (S / D)$$

Where:

$K_{p_{neat}}$  = Skin Permeability Coefficient for the pure substance

$K_{p_{water}}$  = Aqueous Skin Permeability Coefficient

S = Aqueous Solubility (saturated water concentration)

D = Density of the pure substance

At 25°C, the aqueous solubility of MEK is 25.9 mass % = 0.259 g/cm<sup>3</sup> and density is 0.799 g/cm<sup>3</sup> (CRC 2000), resulting in an  $K_{p_{neat}}$  of 0.0016 cm/hr, or 0.000027 cm/min.

Exposed skin surface area was derived as 75% of surface area of both hands, where surface area of both hands was estimated as 5.4% of total skin surface area (Table 8-3 of USEPA 2002b), average of median values for hands as percent of total body surface area for 16-18 year olds). A total skin surface area of 16750 cm<sup>2</sup> was used, calculated as the average of median values for total skin surface area for males and females ages 15-18 (Table 8-1 of USEPA 2002b - 1.75 m<sup>2</sup> and 1.60 m<sup>2</sup>, respectively). Surface area of both hands was then calculated to be 904 cm<sup>2</sup>. Note, this value is greater than surface area of both hands for adults as reported as the USEPA Exposure Factors Handbook (Table 6-4 of USEPA 1997a, mean surface areas of both hands = 840 cm<sup>2</sup> for males, 746 cm<sup>2</sup> for females). Multiplying the total surface area of both hands by 75% (professional judgment), resulted in an exposed skin surface area of 678 cm<sup>2</sup>.

$$\begin{aligned} \text{Thus, } D_{INT} &= \frac{0.8 \text{ g/cm}^3 \times (0.000027 \text{ cm/min}) \times 678 \text{ cm}^2 \times 0.17 \text{ min} \times 1000 \text{ mg/kg}}{67.1 \text{ kg} \times 1 \text{ day}} \\ &= 0.04 \text{ mg/kg/day estimated for a 16-19 year old user.} \end{aligned}$$

This approach is considered a conservative estimate for wood thinners that are solvent mixtures but might contain MEK. Adjusting the dose based upon dermal contact to a chronic basis, assuming a frequency of 12 days out of 365 days per year, yields a potential annual average daily dose of 0.0013 mg/kg/day. For a solvent matrix (USEPA 1992), the solvent skin permeability coefficient can be estimated from the aqueous skin permeability coefficient as:

$$K_{p_{solvent}} = \frac{K_{p_{water}}}{K_{ow}}$$

Where:

$K_{p_{solvent}}$  = Skin Permeability Coefficient for the solvent mixture

$K_{p_{water}}$  = Aqueous Skin Permeability Coefficient

$K_{ow}$  = Octanol-Water Partition Coefficient.

For MEK, the log  $K_{ow}$  = 0.29, yielding a  $K_{ow}$  of 1.95, and a solvent skin permeability coefficient of 0.00256 cm/hr or 1.6 times the pure MEK skin permeability coefficient. This is offset by the lower concentration of MEK in the product mixture. MEK was reported in only one current MSDS for paint thinner at a weight fraction of 25-30%. This concentration is a factor of 3-4 lower than that of pure solvent.

## 5) Product 5. Adhesives

Exposures for adhesive uses were addressed using a hobby model scenario and a scenario based upon adhesive use from Westat(1987). Closed windows were assumed, based upon use information in Westat(1987).

### Scenario A) Hobby Use (Inhalation Exposure)

This scenario was modeled using the latex paint application selection of E-FAST. Details are in Appendix G14.

**Table 8.14 Hobby Model Use of Adhesives - Exposure Modeling Results**

Exposure Scenario		4 hr TWA (mg/m <sup>3</sup> )	Acute Dose Rate (ADR) by age in mg/kg/day						Comments
			<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs	16-19 yrs	
Maximum Use: Day of Use - 40% MEK	Not In Room	0.15	0.008	0.007	0.006	0.005	0.003	0.003	0.45 ACH, for passive child is in same room during use, use 1/2 of a 1 oz container (enough for 5 models as per manufacturer of model adhesive that is 40% MEK)
	In Room	0.43	0.022	0.020	0.017	0.014	0.009	0.008	
Alternate Maximum Use: 100% MEK and complete use of a multiple use-tube; Day of Use	Not In Room	0.05	0.003	0.002	0.002	0.002	0.001	0.001	0.45 ACH, for passive infant is in same room during use, assume 100% MEK, 1 complete 0.07 oz glue, (multiple use specialty glue size, also > amount for 1/2 model as per manufacturer of model adhesive that is 40% MEK)
	In Room	0.15	0.008	0.007	0.006	0.005	0.003	0.003	
			<b>Annual Average Daily Dose (Chronic Dose Rate) by age in mg/kg/day</b>						
Chronic Estimate	Not In Room	-	0.0004	0.0003	0.0003	0.0002	-	-	Chronic estimate using 52 times/year, 12-19 in room, younger not in room, 0.07 oz use, 100% MEK
	In Room	-	-	-	-	-	0.0004	0.0004	

### Scenario B) Hobby Use (Dermal Exposure - Teen only)

Spreadsheet analysis for absorbed dose =

$$D_{INT} = \frac{C \times K_p \times SA \times ED}{BW \times AT}$$

Where  $D_{INT}$  = Internal Dose  
 C = Concentration  
 $K_p$  = Skin Permeability Coefficient  
 SA = Surface Area (exposed skin )  
 ED = Exposure Duration  
 BW = Body Weight  
 AT = Averaging Time

A measured aqueous skin permeability coefficient for MEK is 0.005 cm/hr (USEPA 1992), determined *in vitro* from human skin. USEPA dermal exposure assessment guidance indicates

that full-term infants have completely functional stratum corneum, with excellent barrier properties, thus the measured Kp value is applicable to children and teens (USEPA 1992).

For pure MEK, the skin permeability coefficient can be calculated from the aqueous skin permeability coefficient as (USEPA 1992):

$$Kp_{neat} = Kp_{water} \times (S / D)$$

Where:

Kp<sub>neat</sub> = Skin Permeability Coefficient for the pure substance

Kp<sub>water</sub> = Aqueous Skin Permeability Coefficient

S = Solubility, Aqueous (saturated water concentration)

D = Density of the pure substance

At 25°C, aqueous solubility of MEK is 25.9 mass % = 0.259 g/cm<sup>3</sup> and density is 0.799 g/cm<sup>3</sup> (CRC, 2000), resulting in an Kp<sub>neat</sub> of 0.00016 cm/hr, or 0.000027 cm/min.

A 0.01 cm film of MEK will evaporate in 0.72 minutes (Calculation in Appendix G6), thus 0.72 minutes is used as the event duration. Exposed skin surface area is assumed to be 2 cm<sup>2</sup> (professional judgment), and body weights for 56.6 for a 12-15 year old and 67.1 for a 16-19 year old are used.

$$\text{Thus, } D_{INT} = \frac{0.8 \text{ g/cm}^3 \times (0.000027 \text{ cm/min}) \times 2 \text{ cm}^2 \times 0.72 \text{ min} \times 1000 \text{ mg/g}}{56.6 \text{ kg} \times 1 \text{ day}}$$

for a 12-15 year old, which gives 0.0005 mg/kg/day, and for a 16-19 year old this yields a potential internal dose of 0.0005 mg/kg/day. Similar potential internal doses (0.0003 mg/kg/day both age groups) would be obtained using an estimated solvent skin permeability coefficient and a 40% weight fraction, of MEK as per methodology described in the paint thinner section.

Adjusting the dose based upon dermal contact with pure MEK to a chronic basis, assuming a frequency of 52 days out of 365 days per year, yields potential annual average daily doses of 0.00007 mg/kg/day.

### **Scenario C) Adhesive Use (based upon adult use information in Westat(1997))**

This scenario was also modeled using E-FAST (Appendix G14). Results are:

**Table 8.15 General Use of Adhesives - Exposure Modeling Results**

Exposure Scenario		4 hr TWA (mg/m <sup>3</sup> )	Acute Dose Rate (ADR) by age in mg/kg/day						Comments
			<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs	16-19 yrs	
Maximum Use: Day of Use	Not In Room	1.0	0.05	0.05	0.04	0.03	0.02	0.02	Upper use-56 g, 0.7 weight fraction, 0.45 ACH
	In Room	3.16	0.17	0.15	0.13	0.10	0.06	0.06	
Median Use: Day of Use	Not In Room	0.07	0.004	0.003	0.003	0.002	0.001	0.001	Median use-7 g, 0.35 weight fraction, 0.45 ACH
	In Room	0.19	0.010	0.009	0.008	0.006	0.004	0.003	
			<b>Annual Average Daily Dose (Chronic Dose Rate) by age in mg/kg/day</b>						
Median Use: Chronic Estimate	Not In Room	-	0.0001	0.0001	0.0001	0.00009	0.00006	0.00005	Chronic estimated using median use exposure and 90th percentile of frequency of adult use = 15/year
	In Room	-	0.0004	0.0004	0.0003	0.0003	0.0002	0.0001	

**6) Product 6 - Hobby Model Paints (liquid) - teenage use indoors and infant passive presence**

- i) in the same room during use, and
- ii) elsewhere in house.

This scenario was also modeled using E-FAST (Appendix G14). Results are:

**Table 8.16 General Use of Adhesives - Exposure Modeling Results**

Acute < 1 day Exposure Scenario		4 hr TWA (mg/m <sup>3</sup> )	Acute Dose Rate (ADR) by age in mg/kg/day						Comments
			<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs	16-19 yrs	
Maximum Use: Day of Use	Not In Room	0.14	0.007	0.007	0.006	0.005	0.003	0.002	Used complete 1 oz container, 0.2 weight fraction (28 g), 2 hours, 0.45 ACH
	In Room	0.4	0.02	0.02	0.02	0.01	0.008	0.007	
Median Use: Day of Use	Not In Room	0.07	0.004	0.004	0.003	0.002	0.002	0.001	14 g, 0.2 weight fraction, 45 minutes (active use in room for 1 hour), 0.45 ACH
	In Room	0.20	0.010	0.009	0.008	0.006	0.004	0.004	
			<b>Annual Average Daily Dose (Chronic Dose Rate) by age in mg/kg/day</b>						
Median Use: Chronic Estimate	Not In Room	-	0.0006	0.0005	0.0004	0.0003	-	-	Chronic estimated using median use exposure and assuming frequency of 52 times/year, teens in room, younger not in room
	In Room	-	-	-	-	-	0.0006	0.0005	

**7) Product 7 - Construction Materials and Adhesives**

**Scenario A) New Homes and Cars**

Based upon MEK use information, several indoor air scenarios were identified in which MEK might be elevated. Use of specific consumer products is addressed in separate sections. However, non-specific potential sources of elevated indoor air concentrations include off-gassing of building adhesives and materials in a new home or in a new car. The few studies

identified below reported relatively low concentrations of MEK in new buildings or cars (Table 8.17). Further, several chamber studies of furniture coatings, flooring materials and flooring adhesive materials are summarized in Appendix G4 .

The highest concentration in a new home was 42 ppb (0.124 mg/m<sup>3</sup>) (Hodgson *et al.* 2000). This was a study done on 4 manufactured and 7 site-built houses in the eastern and southeastern United States.

Limited data were available for VOC concentrations in a new car. One study was done with 3 new cars in Australia (1 imported and 2 locally made), which were sampled within 3 days of delivery to purchaser (Brown and Cheng 2000). Analytical results were not reported for MEK alone but for the combined peak of MEK and n-hexane. The maximum combined concentration of MEK and n-hexane was 10 fold < RfC.

**Table 8.17 Indoor Air - New Homes and Cars**

<b>Structure</b>	<b>Level</b>	<b>Reference</b>
New Home: 4 manufactured and 7 site built homes in the US	Geometric mean: 8.8 ppb = 0.026 mg/m <sup>3</sup> Maximum: 42 ppb = 0.124 mg/m <sup>3</sup>	Hodgson <i>et al.</i> 2000
Indoor air of 27 established buildings in Australia, 1-50+ years old, also 4 buildings either new or with new materials	MEK not one of the 35 measurable VOCs reported (> 1 µg/m <sup>3</sup> ). Analytical technique employed was designed to capture a wide boiling point and polarity of VOCs, with high recovery, including VOCs from C5 alkanes, ethanol, and acetone to n-heptadecane.	Brown 2002
New Car	Combined MEK + n-hexane = <1 - 500 µg/m <sup>3</sup> ; Highest value was in one car at 3 weeks; at 9 weeks the value was 34 µg/m <sup>3</sup> in this same car. At first sampling, MEK + n-hexane concentrations were 10, 7.4 and 500 µg/m <sup>3</sup> in Cars 1,2, and 3 respectively.	Brown & Chen 2002

**Scenario B) Pipe Cement and Primer**

Two articles were identified in the secondary literature as indicating the presence of MEK in water due to its use as a pipe cement and primer- Ogawa and Fritz (1985) and Wang and Bricker (1979). Both of these references were obtained and reviewed.

Ogawa & Fritz (1985) reported 1.6 ppb MEK in a drinking water sample (Appendix G4). MEK was nondetect in water from 2 other sources. The article did not mention anything about use of pipe cement.

Wang & Bricker (1979) reported concentrations of up to 4.5 ppm in water. This was a study of laboratory water from an 80 foot of 1.5 inch PVC pipe installed 6-8 months before sample collection. Recovery of MEK was 12% in standards; sample values were corrected for standard recovery. MEK was not detected when there was no residence time in pipe, maximum values reported were associated with a 64-96 hour residence time. Due to the poor analytical recovery, these values were not considered to be correct quantitative estimates of MEK. In addition, the study was performed in conditions (*i.e.*, laboratory setting and multi-day residence

time of water sitting in the pipe) that are not representative of typical residential conditions or water use patterns.

To further investigate the potential for exposure via use of pipe cement and primer, information on usage rates and practices was obtained ([http://members.aol.com/\\_ht\\_a/ezweld](http://members.aol.com/_ht_a/ezweld) ). MEK containing products would be used for plastic pipes. Common practice in the US is to use copper rather than PVC pipes for drinking water intake. In some US areas, use of plastic is not allowed for drinking water piping. However, this is not the case nationwide.

Instructions for using pipe cement and primer were obtained to further assess exposure via drinking water. These instructions indicate that the potential for exposure via the water supply is unlikely to be significant:

- To minimize the amount applied, an applicator is attached to the inside lid of the container.
- After application, pipes must be cured before use. The curing time will depend upon the cement used, size and tolerance of the pipe and fitting, and the air temperature and test temperature. The curing time allows for evaporation of volatile components, and during this process most MEK is likely to be lost. The last fitting will be sealed and so MEK may evaporate into the pipe. The typical practice would be to flush the pipe before use.

Information on amount of pipe cement recommended for use depending upon pipe size and number of fittings, and curing times, is provided in: [http://members.aol.com/\\_ht\\_a/ezweld/ecalc.html?mtbrand=AOL\\_US](http://members.aol.com/_ht_a/ezweld/ecalc.html?mtbrand=AOL_US) and [http://members.aol.com/\\_ht\\_a/ezweld/howto.html?mtbrand=AOL\\_US](http://members.aol.com/_ht_a/ezweld/howto.html?mtbrand=AOL_US). Primer may also be used in the pipe sealing process. However, primer may not be required in pipes under 3" and is not recommended for thin wall, styrene or acrylonitrile-butadiene-styrene (ABS) pipe. When used, primer is used at 1/3 the amount of the pipe cement. This website indicated that to cement six 1" joints, 0.039 quarts of pipe cement should be purchased. Assuming a weight fraction of 45% MEK, this equates to  $0.45 \times 0.052 \text{ quarts} \times 32 \text{ oz/quart} \times 28.3 \text{ g/oz} = 22 \text{ g/MEK}$  for 6 seals (using pipe cement and primer), or 3.6 g/seal. Typical curing for a pipe of this size (1") varies from 1-48 hours depending upon temperature and estimated pressure of use. However, the last piece of pipe will be fitted together without allowing for open air curing.

Assuming that half of the MEK applied at this last juncture is maintained inside the pipe, this results in an estimate of 1.8 g MEK. MEK is soluble in water, and so can partition into it. Vapors that may accumulate would be removed rapidly with the first flush of water through the system. For any remaining MEK, partitioning to flowing water would be minimal due to short contact time with the MEK-containing cement (consistent with Wang & Bricker (1979) which reported MEK was not detected when residence time in the pipe was zero). However, water that is allowed to sit in the pipe could pick up MEK. Given the low amount of MEK likely to remain in the pipe, with proper usage and flushing, extended exposure to elevated MEK is unlikely from this source.

#### 8.7.4 Supplemental Comment on Exposure Methodology and Assumptions

As described in Section 8.7.2, exposure scenarios were developed consistently with USEPA 1992 Guidelines for Exposure Assessment, in that while each individual parameter may not be set at a possible upper bound, the scenario as a whole represents an upper estimate of exposure: "In developing estimates of high-end individual exposure and dose, the following conditions must be met:... not all factors should be set to values that maximize exposure or dose, since this will almost always lead to an estimate that is much too conservative."

For spray products, product mass used and MEK weight fraction in the product are set at upper bounds, and active exposures maintain child presence in the room of use for a one hour period. Room size used for the spray scenarios are a 40 m<sup>3</sup> room (8 feet X 12 feet X 14.5 feet) or a 68 m<sup>3</sup> attached garage (carburetor cleaner), whereas Westat (1987) data indicate that the majority of use for spray paint and carburetor cleaner is outdoors. When spray paint use takes place indoors, it occurs in a range of room sizes, including basements (see Appendix G14, Table G14.3 for detailed information). Information on use location specific to spray wood stain use was not available from the Westat survey, but based upon similar product form and application, may be similar to spray paint. The ventilation rate (Air Changes per Hour, or ACH), is set at an open window but without active ventilation for all 3 spray products, because product characteristics (odor and irritancy) do not support placement in a closed window environment of this size for a one hour duration with an upper use amount. For spray products, due to odor and irritancy, children were considered to be elsewhere in the house for passive exposures.

For paint thinner (a liquid product), 100% MEK was assumed to be used for all scenarios. For addition to a wood stain/varnish, the type of product and amount used is consistent with a floor varnishing scenario. For this scenario, passive child presence in the room of use was considered to be unlikely as the flooring would need to be cleared, and also to avoid contact with the flooring after product application. For hobby model paint use and glue uses, a 40 m<sup>3</sup> room with closed windows was assumed to be the location of use. Acute exposures were estimated for all child age groups both in the room of use and elsewhere in the house. For all scenarios, if use occurred in a smaller home, a greater ventilation rate would be expected due to a greater ratio of external surface area to internal house volume.

Intentional product misuse or use with inadequate ventilation may result in greater exposures; product characteristics, including odor and irritancy, should act as warning properties to minimize time spent under these conditions. If a consumer product containing MEK is used improperly or in a manner not consistent with product label warnings, then effects described on product labels such as headache and nausea may occur, depending upon the circumstances of misuse.

## 8.8 Other Use Categories

The highest estimated consumer product exposures were from aerosol product use. To better understand how uncertainty or variation in model inputs might affect model outputs, a sensitivity analysis was performed on an aerosol use scenario in E-FAST (Appendix G14). This analysis indicated that model output is most sensitive to the amount of material used, weight fraction of MEK in the materials, and the whole house air exchange rate. Further, model output is directly proportional to the amount of material used and also the weight fraction, with a one to one correspondence between changes in these model inputs and model results. Lower model sensitivity was observed for other model inputs. In the exposure modeling done in this assessment, upper estimates of indoor-use product mass and the maximum MSDS weight fraction were used for the upper bound exposure estimates of aerosol consumer products. The sensitivity analysis indicates that lower exposures would be predicted for alternate scenarios in which air exchange rates and product mass or MEK weight fraction were reduced by the same percent from the modeled scenario (as a 50% reduction in product mass or MEK weight fraction would result in a 50% decreased in modeled exposure, but a 50% reduction in air exchange rates would result in <50% increase in modeled exposure). Other Use Categories

### 8.8.1 Food Uses

MEK may be used in preparation of food packaging materials, as a food extractant agent, and as a food-flavoring agent. Residue in food package materials is minimal as per regulatory guidelines (limit of 0.1% by weight in cellophane). These limitations, low mass of cellophane in contact with food, and volatility of MEK indicate this is not likely to be a significant source of MEK exposure.

MEK has Generally Recognized as Safe (GRAS) status and approval for use as a flavoring agent. The amount of MEK that goes into this use is relatively low. WHO (1999) reports the total annual US volume of MEK for use as a flavoring was 190 kg. Fenaroli's Handbook of Flavor Ingredients (Burdock 2002) provides information on reported uses of MEK as a flavoring agent: these values represent the amount of MEK that may be added to the product during processing, they do not represent the amount present in the product upon consumption considering evaporative or degradative losses during processing or time to consumption (T. Adams, Flavor and Extract Manufacturers Association (FEMA), personal communication). WHO recently evaluated and approved MEK for food use (WHO 1999)). Because of its use as a food additive, care was taken to distinguish if food values reported in reviews were from natural occurrence or additive use. The HSDB reported concentrations in ice cream, baked goods and candy from food additive use based upon information from Fenaroli's Handbook of Flavor Ingredients(1975). The most recent version of this handbook (Burdock 2002) reports lower levels for both typical and maximum additive use.

For the population average, Burdock (2002) reports individual ingestion via addition to food at 0.0005932 mg/kg/day. This is based upon reported yearly allotment used as a food additive, divided by the population and assuming 60 kg weight per person. To account for possible underestimation due to incomplete reporting, yearly-consumed mass of MEK is corrected by assuming reported consumption is only 60% of total MEK consumption for food use. Further, to account that not all persons may ingest substances that contain MEK, the rate is calculated by assuming that all food additive MEK is consumed by only 10% of the population. Children may consume greater quantities of some food items that contain MEK as a flavorant as compared to adults. However, even adjusting this by an additional factor of 10 (to consider the potential for greater child consumption of food items which might contain MEK on a body weight basis), yields an average consumption of 0.005932 mg/kg/day.

In addition, WHO (1999) indicates that intake of MEK from natural sources exceeds intake from its use as a flavoring agent. This is based upon a Consumption Ratio analysis. For a given population, the Consumption Ratio is the quantity of a flavoring material consumed as a naturally occurring component in foods divided by the quantity used as a flavoring material over the same time period. This analysis assumes that all flavoring material remains in the final product post processing. For the US population, MEK was shown to be “Food Predominant” meaning that it is consumed predominantly as a naturally occurring ingredient. An analysis which estimated natural consumption based upon only 20 food items resulted in a consumption ratio of >100 (Stofberg and Grunschouer 1987), indicating >99% of dietary MEK intake is from natural occurrence.

An alternate FEMA analysis yields a Possible Average Daily Intake of 2.622 mg/person/day (Burdock 2002). This number is based upon mean consumption values, maximum food additive concentration values, and assuming that the maximum amount of the additive is in the entire food category, not just a substance within that category (for example, an additive to a particular cookie brand would be assumed to occur at the maximum concentration in all baked goods). Because flavoring use is likely to differ among brands and food sources, basing an estimate upon mass of flavoring used per year likely provides a more realistic estimate than developing intake estimates based upon possible concentrations and presence in all items within a food category. This type of analysis will result in an overestimate of potential exposure in particular for MEK, due to its high volatility. For example, natural occurrence of MEK in foods is typically at ppb levels, unless there is a current source of MEK production due to bacterial presence (*i.e.*, cheeses, yogurt, aging food samples and then ppm levels are observed). The concentrations of the food additives used in this assessment are based upon the amount added to the food item, without considering loss during processing and subsequent storage. An additional “reality check” on this assessment can be done by comparing this level of intake with the total annual MEK mass that is sold into this use. A value of 2.622 mg/person/day X 365 days/year = 957 mg/person/year. Given that a total of 190 kg/year MEK is purchased for food flavoring use, and further conservatively assuming that 100% remains in the product to reach the consumer and be ingested, this would indicate that only 199,000 consumers nationwide purchase and ingest all products nationwide to which MEK has been added as a flavorant. This is unlikely to be the case. Further, given a US population of 282,338,631 people (<http://www.census.gov/cgi-bin/ipc/idbsprd>), this would require that 270,198 kg go into food use, with no loss from food before ingestion.

### **8.8.2 Pharmaceuticals**

Further searching was also performed to identify use in the pharmaceuticals category. Information found indicated that MEK is used as a solvent during the synthesis of some pharmaceuticals (USEPA 1997b). Based upon its physical-chemical properties (volatility and biodegradation), MEK is not expected to be found in the final product.

In addition, MEK has been reported to be used as a sterilizing agent for medical products. Again, due to its physical-chemical properties, exposures to individuals would be expected to be minimal.

## **8.9 Overall Summary of Exposure**

Table 8.18 depicts an overall summary of pathways for which exposure was estimated in the children’s exposure assessment.

**TABLE 8.18 Exposure Matrix for Pathways Assessed**

Exposure Route	Children's Environments			
	Car	Residence	Community	School/ Daycare
Inhalation	New car	Ambient air + air in home Residential sources: - New home - Consumer products, scenarios include: Paint thinner/stripper Wood varnish Spray paint Spray primer Hobby paint/glue Adhesive use Automotive product (carb cleaner)	Facility releases	No reason to expect greater background MEK concentrations. Use of a consumer product in a school likely to result in lower exposure than residential setting (larger room size, greater air exchange)
Dermal	-	Inhalation more important, considered dermal contact with paint thinner, hobby glue (liquid products)	-	-
Ingestion	-	Food: Natural levels and flavoring use Water concentrations low as per monitoring data, considered potential exposure via pipe cement use Breast milk - natural	Breast milk-maternal occupational exposure	-

Inhalation exposures that may occur on a chronic (daily, long-term) or intermediate basis (daily but for only a short period of time) are summarized in Table 8.19. Ingestion chronic exposures are summarized in Table 8.20. Acute exposures (inhalation and dermal) are summarized in Table 8.21. Note, chronic exposures (those which occur on a daily basis) lead to low potential for child exposure (lower than RfC or RfD benchmarks defined to be protective of the general population including children). Acute exposures can result in higher acute daily doses. As MEK is rapidly metabolized, acute exposures do not lead to increased body burden over time. Because acute exposures represent events isolated in time, aggregation is not appropriate unless the events occur simultaneously or very close in time.

**Table 8.19 Potential Inhalation Exposures - Chronic and Intermediate Exposures**

Source	Estimate Basis	Concentration (mg/m <sup>3</sup> )	Comments	Likelihood of Exposure
<b>BACKGROUND - Chronic</b>				
Outdoor air- typical	Typical monitoring data	Non-Detect	Low uncertainty- based upon national measured ambient air VOC concentrations, daily averages, exposure assumed for 24 hr/day	
Outdoor air- maximum	Maximum urban/ source monitoring data	0.002 (annual maximum)	Low uncertainty- based upon maximum annual average concentration from USEPA and California monitoring databases.	To reach this exposure would require constant child presence in an urban/source dominated area 24 hr/day.
Indoor Air- Residential	Maximum monitoring data	0.04 mg/m <sup>3</sup> (14 ppb)	Medium uncertainty - based upon limited data set. However, estimate is based upon a maximum value, which is 20-fold greater than lowest value reported.	Exposure to this level on a continuous basis unlikely, as it would require that the maximum short term air concentration be maintained continuously
Indoor Air - School	Not detected in one study, not reported in 2 others	Non-Detect	Very minimal data for schools, but no reason to expect MEK in schools as no sources identified unique to schools, and potential combustion sources ( <i>i.e.</i> , cooking, smoking) are lower in schools than in residences, and greater ventilation and room sizes in schools than in residences (SRD cites ASHRAE for a typical 1.7 ACH for schools)	
<b>SOURCE SPECIFIC - Chronic</b>				
Outdoor Air - Facility Release	Bounding estimate: maximum modeled value using conservative approach	<0.9 mg/m <sup>3</sup>	Based upon assessment of data and conservatism in modeling approach, EPA indicates that maximum exposures are expected to more typically be at least a factor of 2-10 less than 1 mg/m <sup>3</sup>	Exposure to this level on a continuous basis is unlikely, as this is a conservative estimate for areas in close proximity to highest emitting facilities.
	More likely estimate of a maximum value	0.1 - 0.5 mg/m <sup>3</sup>		
<b>SOURCE SPECIFIC - Intermediate</b>				
Indoor Air - New Homes	Maximum value	0.124 mg/m <sup>3</sup>	Limited data. Using the highest measured short-term concentration as an upper bound represents a conservative estimate of chronic exposures.	Measured indoor air values include outdoor air contribution, if any.
	Central tendency value	0.026 mg/m <sup>3</sup>		
Air -New Cars	Maximum value combined MEK and n-hexane	0.5 mg/m <sup>3</sup>	Concentration in the same car was 0.034 mg/m <sup>3</sup> 9 weeks later. Purchase of a new car is a periodic occurrence, and time spent in car is typically a minor portion of the day ( 85 min/day)	Chronic, continuous exposure to this level unlikely

**Table 8.20 - Potential Ingestion Exposures - Chronic and Intermediate**

Summary of exposure in mg/kg/day, by age -									
Exposure	Concentration	<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs	16-19 yrs	Comments	
<b>Background</b>									
<b>Breast milk ingestion</b>	Annual average daily dose, maximum conc.	16.8 ppb	0.0017					Medium uncertainty - based upon concentrations estimated in breast milk -so uncertain, but since breast milk concentrations are taken to be equal to 95th percentile blood concentrations from a general population biomonitoring study, data support this as a conservative upper estimate	
<b>Food - natural occurrence</b>	One day dose	See text for range in values	0.36	0.61	0.39	0.24	0.14	Very uncertain estimate, based upon lack of quantification in many food items and large variation in MEK concentrations across food items in which it has been quantified. Plausible estimate, however, as generally consistent with WHO (1992) estimate which was based upon only a limited number of food items.	
	Annual average daily dose		0.14	0.28	0.23	0.16	0.1		
<b>Specific Sources</b>									
<b>Food flavorant use</b>	Annual average daily dose	WHO analysis	0.0059	0.0059	0.0059	0.0059	0.0059	0.0059	Estimates are uncertain but based upon conservative assumptions- an already conservative analysis based upon standard food safety assessment techniques was adjusted upward by an additional 10-fold factor. There is confidence that this represents an upper bound of potential chronic exposure. Further, WHO has indicated that potential MEK exposure via food flavorant is lower than through natural occurrence (<1% of total MEK intake via food), and since these are a factor of 17-100 below maximum estimates of natural exposure, they seem reasonable as conservative upper bounds of exposure via food from flavorant use
<b>Breast milk ingestion - worst case occupational exposure</b>	Bounding modeled estimate	200 ppm 8 hr/day at work, feeds at work	0.63						Good confidence in this as a bounding estimate, exceeding a plausible upper bound. Uncertainties in breast milk uptake modeling, but conservative estimate based upon 200 ppm exposure, baby breast fed at work, mother's return to work full-time at 2 months of age. Reported occupational exposures are generally well below allowable exposure level, and unlikely for child to be fed directly at work (if brought home, MEK likely to be lost during warming). Exposure via breast milk ingestion not expected at this level (unlikely due to typical workplace practice of limiting solvent exposure for pregnant or nursing women and conservative assumptions), but lower exposures may occur
	Upper estimate	1/4 of above based upon highest 8 hr TWA	0.16						Based upon highest 8-hr TWA exposure (for males). Uncertainty in breast milk exposure modeling, but conservative nature of workplace exposure estimate, along with other conservative assumptions listed above, give confidence in this as an upper estimate

**Table 8.21 - Potential Exposures Associated with Specific Sources, Acute < 1 day Exposures**

Exposure	4 hr TWA-mg/m <sup>3</sup>	Dose Rate by age in mg/kg/day						Comments	Likelihood of Exposure to Source	
		<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs	16-19 yrs			
<b>CARBURETOR CLEANER</b>										
Maximum Use: Day of Use	Passive	1.2	0.07	0.06	0.05	0.04	0.03	0.02	Upper use- 271 g, Garage -68 m <sup>3</sup> , 1.34 ACH, maximum MSDS weight fraction	Indoor use infrequent occurrence for fraction of population.
	Active	3.9	-	-	-	-	-	0.07		
Median Use: Day of Use	Passive	0.3	0.017	0.015	0.013	0.011	0.007	0.006	Median use- 143 g, 1.34 ACH, median MSDS weight fraction	
	Active	1.0	-	-	-	-	-	0.018		
Median Use: Chronic Estimate	Passive	-	0.0003	0.0003	0.0002	0.0002	0.0001	0.0001	Chronic estimated using median and 90th percentile frequency of indoor + outdoor use per year (6), every year	
	Active	-	-	-	-	-	-	0.0003		
<b>SPRAY PAINT</b>										
Maximum Use: Day of Use	Passive	19.9	1.04	0.93	0.81	0.64	0.41	0.35	Upper use-1 can, 40 m <sup>3</sup> room, 1.34 ACH, maximum MSDS weight fraction	Indoor use infrequent occurrence for fraction of population. Frequency for chronic estimate based upon adult use and frequency of all uses (indoor and outdoor). MEK not found in typical spray paints in store visits (more in specialty enamels, auto sprays)
	Active	56.0	-	-	-	-	-	0.99		
Median Use: Day of Use	Passive	9.4	0.49	0.44	0.38	0.30	0.19	0.17	Median use amount, median MSDS weight fraction	
	Active	26.6	-	-	-	-	-	0.47		
Median Use: Chronic Estimate	Passive	-	0.008	0.007	0.006	0.005	0.003	0.003	Chronic estimate using median and 90th percentile frequency of indoor + outdoor uses/yr (6), every year	
	Active	-	-	-	-	-	-	0.008		

**Table 8.21 - Potential Exposures Associated with Specific Sources, Acute < 1 day Exposures**

Exposure	4 hr TWA- mg/m <sup>3</sup>	Dose Rate by age in mg/kg/day							Comments	Likelihood of Exposure to Source
		<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs	16-19 yrs			
<b>WOOD STAINS/ VARNISHES</b>										
Maximum Use: Day of Use	Passive	30	1.59	1.42	1.23	0.98	0.62	0.54	Upper use- 1 can =371 g, 40 m <sup>3</sup> room, 1.34 ACH, maximum MSDS weight fraction- 0.2, (only listed on 1 MSDS)	Indoor use likely infrequent occurrence for fraction of population. Frequency of use for chronic estimate is based upon adults who used this product
	Active	92	-	-	-	-	-	1.62		
<b>PROMISE Modeling run to refine active estimate - details in Appendix G14</b>										
Using maximum amount and weight fraction, PROMISE was run, using conditions which gave same maximum exposure as E-FAST	4 Hr TWA: mean 65 mg/m <sup>3</sup> , 10th-90th percentiles = 26-85 mg/m <sup>3</sup>	For 16-19 year old, day of exposure dose in mg/kg/day: mean = 1.1, median =1.2, 10th-90th = 0.46 - 1.55					This consumer product scenario led to the highest exposures and was refined using the PROMISE model and an estimate of room size distributions for use indoors. The maximum use amount and MSDS weight fraction was still used.			
Median Use: Day of Use	Passive	19	0.98	0.87	0.76	0.60	0.38	0.33	Median use-228 g, 1.34 ACH, 0.2 weight fraction	
	Active	57	-	-	-	-	-	1.00		
Median Use: Chronic Estimate	Passive	-	0.016	0.014	0.012	0.010	0.006	0.005	Chronic estimated using median and 90th percentile frequency of indoor + outdoor use (6/yr), every year	
	Active	-	-	-	-	-	-	0.016		
<b>PAINT THINNER</b>										
<b>Scenario 1: Addition to liquid wood stain/varnish before painting</b>										
Maximum Use: Day of Use	Passive	0.5	0.03	0.03	0.02	0.02	0.01	0.01	Upper use - 3584 g varnish at 0.016 weight fraction MEK (2 oz/gallon), 40 m <sup>3</sup> , 1.34 ACH	Paint thinner use (12/year) seems high for general population. Scenario assumes 100% MEK added to woodstain/varnish. Use likely infrequent occurrence for fraction of population
	Active	1.9	-	-	-	-	-	0.03		
Median Use: Day of Use	Passive	0.03	0.002	0.002	0.001	0.001	0.001	0.001	Median use-454 g varnish at 0.008 weight fraction (1 oz MEK/gallon),40 m <sup>3</sup> , 1.34 ACH	
	Active	0.12	-	-	-	-	-	0.002		
Median Use: Chronic Estimate	Passive	-	5.9E-05	5.3E-05	4.5E-05	3.6E-05	2.3E-05	2.0E-05	Chronic estimated using median and 90th percentile frequency of indoor + outdoor use (12) per year, every year	
	Active	-	-	-	-	-	-	7.0E-05		
<b>Scenario 2: Brush cleaning</b>										
Maximum Use: Day of Use	Passive	0.7	0.038	0.035	0.030	0.024	0.015	0.013	PROMISE model, pure MEK, evaporation from open can, 369 m <sup>3</sup> room (simulated one house-size room), 10 min scenario	Pure MEK is a specialty thinner for particular types of lacquers, and can damage other finishes and plastics. Use of pure MEK for cleaning is likely rare
	Active	13.7	-	-	-	-	-	0.24	PROMISE model, evaporation from open can, 20 m <sup>3</sup> room, 10 min scenario	
Maximum Use: Chronic Estimate	Passive	-	0.0013	0.0011	0.0010	0.0008	0.0005	0.0004	Chronic estimated using 90th percentile frequency of indoor and outdoor use per year, (12) every year	
	Active	-	-	-	-	-	-	0.008		

**Table 8.21 - Potential Exposures Associated with Specific Sources, Acute < 1 day Exposures**

Exposure	4 hr TWA- mg/m <sup>3</sup>	Dose Rate by age in mg/kg/day						Comments	Likelihood of Exposure to Source	
		<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs	16-19 yrs			
<b>Scenario 3: Use in Dermal Clean up</b>										
Maximum Use: Day of Use	Active	-	-	-	-	-	-	0.04	Spreadsheet calculation: 10 sec contact time with 3/4 of each hand	Pure MEK is a specialty thinner for particular types of lacquers, and can damage other finishes and plastics, carries clear warnings (and is more costly than other thinners).
Maximum Use: Chronic Estimate	Active	-	-	-	-	-	-	0.0013	Chronic estimated using 90th percentile frequency of indoor + outdoor use per year (12), every year. Use of pure MEK likely has a lower frequency than that based upon all paint thinners	
<b>ADHESIVES</b>										
<b>Scenario 1: Dermal Exposure during hobby use</b>										
Day of Use	Active	-	-	-	-	-	0.0005	0.0005	Spreadsheet calculation- 0.01 cm film, 2 cm <sup>2</sup> skin surface area, amt absorbed in 43 sec (time to evaporate). 100% MEK	Upper estimate assuming adhesive is 100% MEK
Chronic Estimate	Active	-	-	-	-	-	0.00007	0.00007	Chronic estimate using 52 uses/year (1/week) professional judgment	
<b>Scenario 2: Inhalation during hobby glue use</b>										
Maximum Use: Day of Use - 40% MEK	Not in Room In Room	0.15 0.43	0.008 0.022	0.007 0.020	0.006 0.017	0.005 0.014	0.003 0.009	0.003 0.008	0.45 ACH, for passive, child is in same room during use, use 1/2 of a 1 oz container (enough for 5 models as per manufacturer of model adhesive that is 40% MEK)	Upper estimate assumes windows and doors are closed
Alternate maximum Use: Day of Use- 100% MEK	Not in Room In Room	0.05 0.15	0.003 0.008	0.002 0.007	0.002 0.006	0.002 0.005	0.001 0.003	0.001 0.003	0.45 ACH, for passive, child is in same room during use, 1 complete 0.07 oz glue (multiple use Crazy glue TM size), 100% MEK, (also amount for 1/2 model as per manufacturer of model adhesive that is 40% MEK)	
Alternate Maximum Use: Chronic Estimate	Not in Room	-	0.0004	0.0003	0.0003	0.0002	-	-	Chronic estimated using 52 times/year, 12-19 in room, younger not in room, and the 100% MEK maximum use scenario	
	In Room	-	-	-	-	-	0.0004	0.0004		

Exposure	4 hr TWA- mg/m <sup>3</sup>	Dose Rate by age in mg/kg/day							Comments	Likelihood of Exposure to Source
		<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs	16-19 yrs			
<b>Scenario 3: Inhalation during adult use</b>										
<b>Maximum Use: Day of Use</b>	<b>Not In Room</b>	1.0	0.05	0.05	0.04	0.03	0.02	0.02	Upper use-56 g, 0.7 weight fraction, 0.45 ACH	Upper estimate assumes windows and doors are closed
	<b>In Room</b>	3.2	0.17	0.15	0.13	0.10	0.06	0.06		
<b>Median Use: Day of Use</b>	<b>Not In Room</b>	0.07	0.004	0.003	0.003	0.002	0.001	0.001	Median use-7 g, 0.35 weight fraction, 0.45 ACH	
	<b>In Room</b>	0.2	0.010	0.009	0.008	0.006	0.004	0.003		
<b>Median Use: Chronic Estimate</b>	<b>Not In Room</b>	-	0.0001	0.0001	0.0001	0.00009	0.00006	0.00005	Chronic estimated using median and 90th percentile of frequency of indoor + outdoor adult use = 15/year, every year	
	<b>In Room</b>	-	0.0004	0.0004	0.0003	0.0003	0.0002	0.0001		
<b>HOBBY MODEL PAINTING</b>										
<b>Maximum Use: Day of Use</b>	<b>Not In Room</b>	0.14	0.007	0.007	0.006	0.005	0.003	0.002	Use complete 1 oz container, 0.2 weight fraction, 2 hours, 0.45 ACH	Upper estimate assumes windows and doors are closed
	<b>In Room</b>	0.4	0.02	0.02	0.02	0.01	0.008	0.007		
<b>Median Use: Day of Use</b>	<b>Not In Room</b>	0.07	0.004	0.004	0.003	0.002	0.002	0.001	Use 0.5 (14 g) 0.2 weight fraction, 45 minute use, 0.45 ACH	
	<b>In Room</b>	0.20	0.010	0.009	0.008	0.006	0.004	0.004		
<b>Median Use: Chronic Estimate</b>	<b>Not In Room</b>	-	0.0006	0.0005	0.0004	0.0003	-	-	Chronic estimated assuming frequency of 52 times/year, teens in room, younger not in room	
	<b>In Room</b>	-	-	-	-	-	0.0006	0.0005		

## 9. Risk Assessment

This section uses the information presented in the Hazard Assessment (Section 7) and Exposure Assessment (Section 8) to assess the potential risks to children from reasonably anticipated exposures to MEK. The Exposure Assessment describes natural as well as man-made sources of exposure to MEK. Natural sources include endogenous production via metabolism, natural presence in the environment, and natural presence in food. This risk assessment focuses primarily on potential exposures to children from man-made sources, including the following (some of which also encompass exposure from natural sources):

- Outdoor air (ambient levels and facility emissions)
- Indoor air
- Water
- Soil
- Breast milk – occupationally-exposed mother
- Consumer products

The risk assessment begins with a brief recap of the hazard information and relevant health benchmarks, and then addresses potential children's exposures under the relevant scenarios. The discussion of potential exposures from consumer products includes a chronic hazard evaluation and a separate discussion of one-day (single-event) exposures. Uncertainties also are discussed, and overall conclusions are presented concerning the potential for MEK to pose health risks to children from reasonably anticipated exposures.

### 9.1 Overview of Hazard Information and Relevant Health Benchmarks.

As described in the Hazard Assessment (Section 7), MEK has low acute and chronic toxicity. The concern for developmental and reproductive toxicity is low, and MEK is not neurotoxic. MEK also is not genotoxic and is not likely to be carcinogenic. These conclusions are consistent with prior regulatory assessments and other peer-reviewed assessments (described in Section 3).

The key health benchmarks for this risk assessment are the inhalation reference concentration (RfC) of 5.0 mg/m<sup>3</sup> and oral reference dose (RfD) of 0.6 mg/kg/day posted by EPA on the IRIS database. These values, as a matter of EPA policy, are intended to represent exposures that may be continued for a lifetime for the general population, including children and other sensitive subgroups, without appreciable risk of adverse effects.

Continuous inhalation exposures, such as may occur from levels of MEK in ambient air, will be compared to the RfC. Potential oral exposures will be compared to the RfD. Chronic exposures from intermittent use of individual products have been expressed in mg/kg/day and will be compared to the oral RfD. Single-event exposures also are compared to the NOAEL of 200 ppm established in 4-hour human studies sponsored by NIOSH.

### 9.2 Ambient Exposures – Air, Water and Soil

#### 9.2.1 Ambient Air

Levels in ambient air are described in Section 8.5.1. Generally, MEK has not been detected or has been detected at very low levels, in the range of a few parts per billion or less. These levels are well below EPA's inhalation RfC of 5.0 mg/m<sup>3</sup> (approximately 1.7 ppm), which is intended to

represent a level to which the general population, including sensitive subgroups, may be exposed continuously for a lifetime without appreciable risk. Accordingly, exposures to MEK from ambient air should not be expected to pose health risks to children.

### **9.2.2 Indoor Air**

The same conclusion applies to exposures to MEK in indoor air, which also are described in Section 8.5.1. Where detected, MEK has been present in indoor air in the low parts per billion range, far below the proposed RfC, and therefore far below levels that might pose a health concern.

### **9.2.3 Water**

MEK generally has not been detected in drinking waters or potential sources of drinking water (surface or groundwater), see Section 8.5.1. A 1985 publication reports a single confirmed value of 1.6 ppb MEK in a drinking water sample. Even assuming that all water contains MEK at that concentration, for a child who consumes one liter of water per day, the estimated daily consumption would be only 1.6 µg. For a child of any age, the exposure expressed in mg/kg/day would be orders of magnitude below the RfD of 0.6 mg/kg/day. Accordingly, potential exposures from low levels of MEK that may occur (rarely) in sources of drinking water are deemed to be insignificant.

### **9.2.4 Soil**

A literature search did not identify any measurements of MEK in soil (other than landfills or waste sites), see Section 8.5.1. Given MEK's physical and chemical properties, it would not be expected to persist in soil. Thus, the potential for children's exposure to MEK in soil appears minimal.

## **9.3 Exposures from Facility Releases**

Environmental releases from industrial facilities are described in Sections 5.5 and 8.6.1. Releases to soil and water are minor and should not be expected to result in significant exposures. Releases to air have been evaluated recently by EPA's Office of Air Quality and Planning Standards (OAQPS) in connection with its review of a petition to remove MEK from the list of hazardous air pollutants (HAPs) regulated under the CAA. EPA has proposed to grant that petition, based on a determination that facility releases may not reasonably be anticipated to result in adverse human health or environmental effects. EPA's evaluation of facility releases is summarized in Sections 3.3 and 8.6.1.

EPA's assessment was based on extensive air dispersion modeling performed by petitioners using EPA-approved techniques that incorporated numerous conservative assumptions. Based on this information, EPA concluded that maximum modeled annual average air concentrations are below 0.9 mg/m<sup>3</sup>, and actual human exposures are likely to be below modeled air concentrations by as much as an order of magnitude or more. Thus, maximum modeled air concentrations are expected to be well below the RfC, and actual exposures are expected to be much lower, and for most of the general population likely are 100-fold (or more) below the RfC. On this basis, one can conclude, as EPA has recently done, that facility releases may not reasonably be expected to pose any health risks.

#### **9.4 Exposure to Children Via Occupationally Exposed Parents**

Potential exposures to children from occupationally exposed parents are described in Section 8.6.2. The potential for transfer of MEK to a child from parental skin or clothing is deemed minimal because MEK's relatively high vapor pressure and ready evaporation likely would cause any MEK to dissipate before contact at home could occur. The exposure assessment therefore focused on potential exposure to MEK in breast milk of an occupationally exposed mother. The assessment was based on several conservative assumptions:

- Exposure at the OSHA PEL and ACGIH TLV of 200 ppm for the entire 8-hour work day;
- Exposure continues at that level 5 days/week for 40 weeks (10 months);
- Mean ingestion rate of 688 ml/day breast milk per day (US EPA Exposure Factors Handbook (1997));
- Mother nurses infant at regular intervals while at work; and
- Infant body weight of 7.8 kg.

Even with these conservative assumptions, the estimated ingestion (presented in Section 8.6.2) was only 0.63 mg/kg/day, which is essentially equal to the RfD. (The RfD is based on a point of departure of 639 mg/kg/day, to which total uncertainty factors of 1000 were applied, producing a value of 0.639, mg/kg/day, which was rounded off to 0.6 mg/kg/day. (See Toxicology Review of Methyl Ethyl Ketone (2003) at pp. 70-72.) Actual exposures are expected to be much lower than this upper bound estimate.

Using an assumed workplace exposure level of 45 ppm (highest occupational 8 hr TWA reported in HSDB 2001) produced an estimate of 0.16 mg/kg/day. Workplace exposures typically are expected to be below the highest level of 45 ppm level reported in HSDB.

Further, exposures via breast milk from an occupationally exposed mother would be much lower if feeding did not occur at the workplace. If breast milk were expressed and refrigerated for later use, much of the MEK likely would be lost when the milk was warmed.

In summary, using the oral RfD of 0.6 mg/kg/day as the relevant health benchmark, it is apparent that even upper bound estimates of potential exposure to MEK in breast milk of an occupationally exposed mother are at or below the RfD, and thus actual exposures are likely to be well below levels that might pose health concerns.

#### **9.5 Potential Exposures from Consumer Products**

Potential children's exposures were assessed for several categories of consumer products and consumer product uses scenarios:

- carburetor cleaner;
- spray paint;
- wood stain/varnish;

- paint thinner – added to coating;
- paint thinner –brush clean-up
- paint thinner – personal clean-up (dermal exposure)
- adhesives – hobby use
- adhesives – hobby use (evaporation from open container);
- adhesives – adult use;
- hobby model paints;
- indoor air from building materials used in new cars and homes;
- food uses (food flavorant).

In some cases, children of the appropriate age group were assumed to have direct exposure from use of the product. In other cases, an adult was assumed to use the product, and children were assumed to have secondary (passive) exposure from presence in the same room or another room in the house. Exposures were estimated for the day of use and from repeated use over time (chronic exposure).

#### **9.5.1 Potential Chronic Exposures from Consumer Products**

Conservative estimates of potential chronic exposures, expressed in mg/kg/day, are summarized in Table 9.1 and compared to the oral RfD of 0.6 mg/kg/day. (The values are taken from Table 8.21.) The chronic estimates are based upon a 90<sup>th</sup> percentile use frequency occurring each and every year, assume all product use is indoors, and MEK is present in all products used. In every case, potential chronic exposures are well below the RfD for all age groups. Margins of safety range from 37.5 to 30,000. Margin of safety (MOS) is determined by dividing the proposed oral RfD of 0.6 mg/kg/day by the estimated exposure for each age group. Since lifetime exposure at the RfD is deemed to be without appreciable health risks, any MOS of 1 or greater is indicative of no likely health risk. Accordingly, repeated use of these products over time should not be expected to pose significant health risks to children in any age group.

**Table 9.1 Children's Potential Chronic Exposures to MEK  
from Selected Consumer Product Use Scenarios**

Use Scenario		Exposure by Age Group (mg/kg/day)						Margin of Safety <sup>1</sup>
		<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs	16-19 yrs	
<b>Carburetor Cleaner</b>	Passive	0.0003	0.0003	0.0002	0.0002	0.0001	0.0001	2,000 to 6,000
	Active						0.0003	2000
<b>Spray Paint</b>	Passive	0.008	0.007	0.006	0.005	0.003	0.003	75 to 200
	Active						0.008	75
<b>Wood Stains/Varnishes</b>	Passive	0.016	0.014	0.012	0.010	0.006	0.005	37.5 to 120
	Active						0.016	37.5
<b>Paint Thinner</b>								
<b>Scenario 1: Addition to liquid wood stain/varnish before painting</b>								
	Passive	5.9E-05	5.3E-05	4.5E-05	3.6E-05	2.3E-05	2.0E-05	10,169 to 30,000
	Active						7.0E-05	8,571
<b>Scenario 2: Brush cleaning</b>								
	Passive	0.0013	0.0011	0.0010	0.0008	0.0005	0.0004	462 to 1500
	Active						0.008	75
<b>Scenario 3: Use in Dermal Clean Up</b>								
	Active only						0.0013	462
<b>Adhesives</b>								
<b>Scenario 1: Dermal Exposure during hobby use</b>								
	Active					0.00007	0.00007	8,571
<b>Scenario 2: Inhalation during hobby glue use</b>								
	Not in Room	0.0004	0.0003	0.0003	0.0002			1,500 to 3,000
	In Room					0.0004	0.0004	1,500
<b>Scenario 3: Inhalation during adult use</b>								
	Not in Room	0.0001	0.0001	0.0001	0.00009	0.00006	0.00005	6,000 to 12,000
	In Room	0.0004	0.0004	0.0003	0.0003	0.0002	0.0001	1,500 to 6,000
<b>Hobby Model Painting</b>								
	Not in Room	0.0006	0.0005	0.0004	0.0003			1,000 to 2,000
	In Room					0.0006	0.0005	1,000 to 1,200

<sup>1</sup> Margin of safety (MOS) is determined by dividing the proposed oral RfD of 0.6 mg/kg/day by the estimated exposure for each age group. Since lifetime exposure at the RfD is deemed to be without appreciable health risks (see Section 7.13), any MOS of 1 or greater is indicative of no likely health risk.

### 9.5.2 Single-Day Exposures from Consumer Products

The principal concern for short-term exposures to MEK pertains to its potential to cause sensory irritation. As described in Section 7.12, studies sponsored by NIOSH and conducted by Dick *et al.* provide a NOAEL of 200 ppm (590 mg/m<sup>3</sup>) for sensory irritation for exposures up to four hours. A NOAEL of 200 ppm also was reported by Muttray *et al.* (2002). This NOAEL is assumed to apply equally to children. EPA has stated, "We would expect the same nonadverse effect concentrations to be relevant for children, as there is no reason to consider children as a sensitive subgroup for such a highly subjective, nonadverse effect as mild irritancy."<sup>69</sup>

Table 9.2 presents 4-hour time-weighted average (TWA) exposures to MEK from all the consumer product use scenarios addressed in the previous discussion of chronic exposures. Values are calculated for "maximum use" and "median use" scenarios, and are explained in Section 8 and Appendix G14. All 4-hour TWAs are significantly below the NOAEL of 200 ppm (590 mg/m<sup>3</sup>) established by Dick *et al.*, indicating low concern for potential acute effects from use of these products.

As reflected in Appendix G14, some product use scenarios are assumed to last less than 4 hours, and thus exposure concentrations during actual use of the products may be higher than the stated 4-hour TWA values. However, when proportional adjustments are made to the 4-hour TWAs, all values are still below the NOAEL of 200 ppm established by Dick *et al.*

MEK's strong odor serves as a useful warning property against excessive short-term exposures. As described in Section 7.12, test subjects in the NIOSH studies by Dick *et al.* found the "strong odor" at 200 ppm to be objectionable. Additionally, product labels for products that contain high concentrations of solvents typically use large bold type to direct consumers to use the product only in a well-ventilated area similar to outdoor conditions. (See related discussion in Section 8.7 and pictures in Appendix G13.) The exposure assessments presented in Section 8 are conservative and likely understate ventilation. These are additional reasons to believe proper use of MEK-containing products will not pose acute health risks to children.

Intentional misuse and abuse situations are not addressed in this exposure assessment and are assumed to be potentially harmful. Also, if products are used without proper ventilation or otherwise in a manner not consistent with label warnings, then sensory irritation or other effects described in typical product warnings (e.g., headache, nausea) may occur, depending on the circumstances of improper use.

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<sup>69</sup> See 68 Fed. Reg. 32606, 32614 (May 30, 2003) (CAA delisting proposal).

**Table 9.2 Children's Potential Acute Exposures to MEK from Selected Consumer Product Use Scenarios**

Use Scenario		4 hr TWA- mg/m <sup>3</sup>	Margin of Exposure <sup>70</sup>
<b>Carburetor Cleaner</b>			
Maximum Use	Passive	1.2	492
	Active	3.9	151
Median Use:	Passive	0.3	1967
	Active	1.0	590
<b>Spray Paint</b>			
Maximum Use	Passive	19.9	30
	Active	56.00	11
Median Use:	Passive	9.4	63
	Active	26.6	22
<b>Wood Stains/Varnishes</b>			
Maximum Use	Passive	30	20
	Active	92	6
Median Use	Passive	19	31
	Active	57	10

<sup>70</sup> Margin of exposure (MOE) is determined by dividing the NOAEL for sensory irritation by the estimated 4-hour TWA exposure for each use scenario. The NOAEL for sensory irritation is 200 ppm (590 mg/m<sup>3</sup>), based on 4-hour exposures to human volunteers, as reported by Dick et al. (1992) and Muttray et al. (2002).

Use Scenario		4 hr TWA- mg/m <sup>3</sup>	Margin of Exposure <sup>70</sup>
<b>Paint Thinner</b>			
<b>Scenario 1: Addition to liquid wood stain/varnish before painting</b>			
Maximum Use	Passive	0.5	1180
	Active	1.9	311
Median Use	Passive	0.03	19666
	Active	0.12	4917
<b>Scenario 2: Brush cleaning</b>			
Maximum Use	Passive	0.7	843
	Active	13.7	43
<b>Adhesives</b>			
<b>Scenario 1: Inhalation during hobby glue use</b>			
Maximum Use	Not in Room	0.15	3933
Hobby model glue at 40% MEK	In Room	0.43	1372
Alternate Maximum Use	Not in Room	0.05	11800
100% MEK, 0.07 oz used	In Room	0.15	3933

Use Scenario		4 hr TWA- mg/m <sup>3</sup>	Margin of Exposure <sup>70</sup>
<b>Scenario 2: Inhalation during adult use</b>			
Maximum Use	Not In Room	1.0	590
	In Room	3.2	184
Median Use	Not In Room	0.07	8429
	In Room	0.2	2950
<b>Hobby Model Painting</b>			
Maximum Use	Not In Room	0.14	4214
	In Room	0.4	1475
Median Use	Not In Room	0.07	8429
	In Room	0.20	2950

## 9.6 Potential for Aggregate Exposures at Levels of Concern

Chronic exposures have been estimated for selected consumer product use scenarios believed to represent the highest potential for exposure. Looking at the consumer product use scenarios addressed in Table 9.1, it is readily apparent that potential aggregate chronic exposures for those uses for all age groups are below the RfD. The potential for aggregate chronic exposures from all sources to pose significant health risks is considered remote. Key points include:

- MEK is eliminated from the body very quickly.
- Exposures from anthropogenic sources that children are expected to encounter on a daily basis (e.g., indoor and outdoor air, sources of drinking water, food) are very low, and in particular well below the RfC and RfD.
  - The inhalation RfC is 5 mg/m<sup>3</sup>. The highest measured MEK air concentrations are 0.002 mg/m<sup>3</sup> for an annual average, and 0.04 mg/m<sup>3</sup> for short-term indoor or outdoor air measurements. Based upon a conservative modeling analysis, EPA concluded that potential ambient exposures due to facility emissions may not reasonably be anticipated to cause adverse human health effects (upper exposure estimates of 0.1-0.5 mg/m<sup>3</sup>). Intermediate exposures (exposures which may be encountered daily over a short period of time) were also low in comparison to the RfD: a maximum of 0.124 mg/m<sup>3</sup> for a new home (0.026 mg/m<sup>3</sup> central tendency value), and a maximum combined value of 0.5 mg/m<sup>3</sup> in a new car for MEK+ another analyte (unresolved analytical peak). The intermediate exposures would only be encountered for the portion of each day spent in the specific environment, and MEK concentrations would decrease over time. Even in aggregate, these exposures are well below the RfC.
  - The oral RfD is 0.6 mg/kg/day. Potential ingestion via food flavoring use is estimated at 0.0059 mg/kg/day. For an occupationally exposed mother, a bounding estimate of infant MEK ingestion via breast milk, based upon the highest reported 8-hr TWA, and assuming infant is present at work to breast feed, was 0.16 mg/kg/day. Monitoring data and/or physicochemical properties indicate that drinking water and soil ingestion are not significant exposure pathways.
- Exposures from representative consumer products – products that are believed to represent the high end of potential exposures – are quite low by comparison to the RfD. Estimated chronic exposures in most cases are less than 1 percent of the RfD.
  - The 16-19 year old age group had the highest active exposure estimates of any of the child age groups. Assuming that the child actively used all of the following products indoors during one year, and that MEK was present in all product brands used, would result in a total chronic exposure of 0.035 mg/kg/day:
    - Carburetor cleaner in attached garage, 6X
    - Spray paint, 6X
    - Aerosol woodstain/varnish, 6X

- 100% MEK paint thinner added to liquid varnish, 12X
  - 100% MEK used to clean paint brushes, 12X
  - Paint thinner used to clean hands (dermal), 12X
  - Adhesives during hobby use (inhalation and dermal)- 52X
  - Adhesives during adult use (inhalation)- 15X
  - Hobby paint use - 52X
- The infant age group (<1 year) had the highest passive exposure estimates of any of the child age groups. This is due to inhalation being the main MEK exposure route, and infants having a greater inhalation rate on a body weight basis ( $\text{m}^3/\text{kg}/\text{day}$ ) than older age groups. Assuming that an infant is present in the house during the following indoor uses, and that MEK is present in each product brand used, would result in a total chronic exposure of 0.027 mg/kg/day:
  - Carburetor cleaner in attached garage, 6X
  - Spray paint, 6X
  - Aerosol woodstain/varnish, 6X
  - 100% MEK paint thinner added to liquid varnish, 12X
  - 100% MEK used to clean paint brushes, 12X
  - Adhesives during hobby use - 52X
  - Adhesives during adult use - 15X
  - Hobby paint use - 52X
- Most products that have been identified as containing MEK are not intended for use by children, such that children's exposure typically would occur, if at all, through the child's presence in the room where the product is used or somewhere else in the home.
- Most products that have been identified as containing MEK typically are used only on an intermittent basis, and not by all persons. Whereas product use information indicated that periods of greater than a year could elapse between uses, the estimated chronic exposure values assumed a 90<sup>th</sup> percentile use frequency for each and every year.
- Analysis of consumer products indicated that MEK is typically present in only a fraction of available brands for a given type of product. Chronic exposure values were estimated assuming MEK was present in 100% of the brands for each product.

Based on the foregoing points, there is no reason to anticipate that use of multiple products would cause children's exposures to exceed the RfC or RfD. There does not appear to be a reasonable basis for concern that multiple sources of MEK exposures might in the aggregate pose significant health risks to children.

### **9.7 Discussion of Uncertainties**

Uncertainties in the exposure estimates are described in Section 8 and related appendices. Uncertainties in the derivation of the RfD and RfC values are described in the IRIS draft documents. Neither the hazard assessment nor the exposure assessment is an exact science, but conservative (*i.e.*, health protective) assumptions are employed in each area, such that margins of safety are more likely to be understated than overstated. Because estimated exposures are below the relevant health benchmarks, there is no need to reduce any of the uncertainties inherent in the hazard or exposure assessments. See further discussion in Section 10 -- Data Needs Assessment.

### **9.8 Conclusion**

The hazard and exposure information presented in this document demonstrate that reasonably anticipated children's exposures to MEK from intended uses of consumer products containing MEK, and from other expected sources, are unlikely to pose significant health risks.

## **10. Data Needs Assessment**

### **10.1 Hazard Information**

Most of the Tier 1, Tier 2 and Tier 3 studies included in the VCCEP program have been conducted for MEK or its metabolic precursor, sBA. For reasons presented in Section 7 (Hazard Assessment), the VCCEP sponsors believe available data from the progressive and methodical evaluation of MEK do not indicate likely hazards in the areas of immunotoxicity, developmental neurotoxicity or chronic toxicity/oncogenicity. Further testing is scientifically unnecessary. Concerning the potential for immunotoxic effects, the weight of evidence in the dermal irritation/sensitization studies (including humans), and the multiple repeated-dose animal studies with MEK and/or sBA indicates that these compounds are neither allergens nor immunosuppressants, indicating no need for further immunotoxicity testing. Also, the structural analog acetone (methyl methyl ketone) has recently been tested for immunotoxic effects and was negative.

The totality of scientific evidence available for MEK also is not suggestive of a developmental neurotoxicity hazard. Animal and human studies do not indicate MEK is neurotoxic, and developmental toxicity studies have not indicated neurological effects on offspring. Since MEK is not considered a primary developmental toxicant, nor neurotoxic, it is highly unlikely to be a developmental neurotoxicant. Finally, while MEK has not been tested specifically for carcinogenicity, data on its structure and metabolism, low subchronic toxicity and negative genotoxicity data all support the conclusion, accepted by EPA in other settings, that MEK is unlikely to be carcinogenic.

The VCCEP sponsors' conclusion that further testing is not necessary is consistent with the OECD SIDS assessment and EPA's prior assessment under TSCA (when chronic testing was determined to be not necessary). Further, the existing data have been found sufficient for the derivation of an inhalation RfC and oral RfD, and the exposure assessment demonstrates that reasonably anticipated exposures are below these conservative health benchmarks, in most cases by very large margins. In summary, existing studies demonstrate that MEK has low acute and systemic toxicity, and there would appear to be no scientific justification for conducting additional toxicology studies of MEK.

### **10.2 Exposure Information**

For a compound like MEK, additional exposure assessment work is always possible. The VCCEP sponsors believe, however, that the information presented in this document is adequate to demonstrate that reasonably anticipated exposures to MEK are not likely to exceed relevant health benchmarks and are not likely to present significant health risks to children. Accordingly, the VCCEP sponsors believe additional exposure assessment work also should be a low priority, and is not necessary to meet the objectives of the VCCEP program.

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